Foundation for the National Institutes of Health

Researching COVID to Enhance Recovery - Treating Long COVID (RECOVER-TLC)

Navigating the Pathway Forward

September 23 – 25, 2024

Revised December 13, 2024

This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the Foundation for the National Institute of Health (FNIH). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of FNIH. Contributions to this summary by the following individuals are gratefully acknowledged: Cecelia Garcia, Juliana Piacentini, Cooper Roache, Kelly Beazley, and Cherie Dewar.

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Acronym List

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
AHRQ	U.S. Agency for Healthcare Research and Quality
ASPR	Administration for Strategic Preparedness and Response
BLA	biologics license application
CDC	U.S. Centers for Disease Control and Prevention
CDE	common data element
COA	clinical outcome assessment
COMPASS-31	Composite Autonomic Symptom Score-31
CRP	c-reactive protein
EHR	electronic health record
EMA	European Medicines Agency
EPICC	Emerging Infectious Diseases with Pandemic Potential
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
FND	functional neurological disorder
FNIH	Foundation for the National Institutes of Health
HHS	U.S. Department of Health and Human Services
IACC	infection-associated chronic condition
IND	investigational new drug
IRB	institutional review board
IVIG	intravenous immunoglobulin
LIINC	Long-term Impact of Infection with Novel Coronavirus
MCAS	mast cell activation syndrome
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
MHS	military health system
MIS-C	multisystem inflammatory syndrome in children
MOA	mechanism of action
NASEM	National Academies of Sciences, Engineering, and Medicine
NCATS	National Centers for Advancing Translational Sciences, NIH
NDA	new drug application
NET	neutrophil extracellular trap
NHLBI	National Heart, Lung, and Blood Institute, NIH
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke, NIH
OASH	Office of the Assistant Secretary for Health, HHS
PASC	postacute sequelae of SARS-CoV-2 infection
PBMC	peripheral blood mononuclear cell
PECOS	Pediatric COVID Outcomes Study
PEM	post-exertional malaise
PET	positron emission tomography

PoC	people of color
POTS	postural-orthostatic tachycardia syndrome
PROs	Patient-reported outcomes
REACT	Real-time Assessment of Community Transmission
RECOVER	Researching COVID to Enhance Recovery
REVERSE-LC	Randomized Double-Blind Placebo-Controlled Trial Evaluating Baricitinib on Persistent Neurological and Cardiopulmonary Symptoms of Long COVID
RECOVER-Pediatrics	RECOVER Pediatric Observational Cohort Study
RECOVER-TLC	Researching COVID to Enhance Recovery-Treating Long COVID
SES	socioeconomic status
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
SIMOA	single molecule assay
SMEs	subject matter experts
SNX8	sorting nexin 8
SOC	Scientific Oversight Committee
STOP-PASC	Selective Trial of Paxlovid for Postacute Sequelae of SARS-CoV-2 Infection
TOPMed	Trans-Omics for Precision Medicine
UCSF	University of California San Francisco
UCTD	undifferentiated connective tissue disease
VA	U.S. Department of Veterans Affairs
WG	working groups

Workshop Summary

Welcome and Opening Remarks

Dr. Monica Bertagnolli, National Institutes of Health (NIH); Dr. Julie Gerberding, Foundation for the National Institutes of Health (FNIH)

This Researching COVID to Enhance Recovery -Treating Long COVID (RECOVER-TLC) meeting, supported by the National Institute of Allergy and Infectious Diseases (NIAID) and FNIH, welcomed more than 1,200 virtual and 180 in-person participants representing research institutions, industry, federal agencies, patient advocacy groups, caregivers, and patients. Following the acknowledgement of Long COVID as a medical condition in 2020, NIH-sponsored research has increased our understanding of Long COVID symptoms, its risk factors, and the health disparities that influence the development of Long COVID. However, Long COVID encompasses over 200 conditions, and additional research is needed to understand its underlying pathobiology, as well as to develop diagnostics and identify safe and effective treatments for Long COVID. This meeting aims to identify gaps in our scientific and clinical knowledge about Long COVID, increase transparency in research, encourage flexible and inclusive efforts in response to new knowledge, and foster partnerships across federal agencies, research organizations, industry organizations, people living with Long COVID, and those caring for individuals with Long COVID.

Goals of the Workshop

Dr. Jeanne Marrazzo, NIAID; Dr. Lindsey Baden, Brigham and Women's Hospital (BWH), Harvard University

RECOVER-TLC seeks to alleviate the suffering of people with Long COVID by contributing to the development of safe and effective therapeutic interventions for Long COVID and associated illnesses and by providing these interventions to care providers and their patients as rapidly as possible. In support of these goals, the RECOVER-TLC Workshop will provide a high-level scientific review of clinical data and pathobiological mechanisms from global experts, addressing four key RECOVER-TLC scientific aims: (a) identify pharmacologic and nonpharmacologic interventions for treating Long COVID; (b) build on findings from previous research efforts, including ongoing RECOVER cohorts and clinical trials; (c) develop clinical trials with direct and transparent engagement from both scientific leaders and patient communities; and (d) encourage rapid data sharing throughout the scientific community and broader public. Guiding these aims are core principles that patients should be central to research efforts; studies should be inclusive and diverse; community engagement should be encouraged; research should use standardized methods (e.g., platform protocols) and common data elements (CDEs); and scientific communities should be aware of and continue to adapt to rapid research and clinical developments. Further, research should involve underrepresented and at-risk groups, including pediatric, pregnant, lactating, and immunocompromised individuals. Presentations and discussion topics at the Workshop addressed pathobiology, biomarkers,

epidemiology, cohort studies, complexities in trial design, prioritization of interventions, and the identification of meaningful and informative study endpoints.

NIAID recognizes the wide, multisystem clinical spectrum of Long COVID that has globally impacted over 400 million individuals and has resulted in an annual economic impact of $1 trillion. The complexities of this multisystem disorder, along with its substantial impact on lives, have led several Federal agencies and scientific institutions to collaborate and adopt a multidisciplinary approach to support research efforts and build crucial relationships with patients and advocacy groups. These collaborating Federal agencies include the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Neurological Disorders and Stroke (NINDS), the National Center for Advancing Translational Sciences (NCATS), and NIAID, that support large-scale clinical trials Additionally, the U.S. Food and Drug Administration (FDA) provides regulatory expertise.

RECOVER-TLC will hold annual meetings and periodic webinars, as well as send newsletters to disseminate research findings and identify new areas of interest related to Long COVID.

RECOVER-TLC—Proposed Organizational Structure and Function

Dr. Joseph Breen, NIAID

RECOVER-TLC is committed to using a patient-centered, inclusive, national-scale approach to support Long COVID research efforts, building on similar approaches (e.g., platform protocols and adaptive approaches based on emerging science) that contributed to the success of Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). To improve transparency and integration, the proposed RECOVER-TLC organizational structure was designed to ensure community engagement, subject matter expertise, clinical trial oversight, and rapid dissemination of research findings.

RECOVER-TLC will establish scientific working groups (WGs), based on COVID's mechanisms of disease (e.g., neurology, cardiovascular, virology) and its symptoms, to identify potential biologics and therapeutics for further study. These WGs will report recommendations of agents to be prioritized to the Scientific Oversight Committee (SOC), which will include subject matter experts (SMEs) and community members. The SOC will assess lists of these agents and make a recommendation to the Executive Committee (EC) regarding which should be evaluated in a clinical trial.

Parallel to these SOC efforts, the Operations Oversight Group will leverage NIAID resources to design and conduct clinical trials of SOC-prioritized agents while ensuring that vulnerable groups, such as pediatrics, pregnant and lactating people, and diverse populations, are included within clinical trial designs. Both the SOC and Operations Oversight Group will identify targets for future research, as well as convey clinical trials results and other information to the EC.

The RECOVER-TLC EC, consisting of the NIH Director, NIAID Director, NHLBI Director, NINDS Director, and FNIH President, will decide whether to proceed with clinical trials of prioritized therapeutics and biologics.

Underscoring the critical role of community engagement in Long COVID research, RECOVER-TLC will establish a Community Engagement Group that will provide feedback directly to the EC, participate in all WGs and the SOC, and discuss agent prioritization. Additionally, these efforts will be supported by an Agent Submission Portal, launched on September 30, 2024, to allow community members to submit areas of interest for further study.

Living with Long COVID—Diverse Perspectives

Christine Maughan, Patient Representative; Angela Meriquez Vazquez, Children's Partnership; Liza Fisher, Patient Advocate

Christine Maughan

Ms. Maughan shared that in March 2020, she began experiencing symptoms of COVID-19. Early symptoms included a rash and impaired taste that was followed by labored breathing and eventual hospitalization. Today, Ms. Maughan continues to experience symptoms, including tachycardia, dizziness, tremors, joint and muscle pain, chest pain, shortness of breath, fatigue, increased susceptibility to fevers, and post-exertional malaise (PEM). She also has been diagnosed with several infection-associated chronic conditions (IACCs), including post-orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and undifferentiated connective tissue disease (UCTD).

Ms. Maughan was extremely active prior to contracting SARS-CoV-2, the virus that causes COVID-19. At 37 years old, she was an endurance cyclist, avid skier and hiker, and she was active within her community, volunteering at her daughter's school and serving on the board of a nonprofit organization. Once able to hike mountains, Ms. Maughan now requires a wheelchair to navigate airports, and daily activities are carefully considered to minimize symptoms. She frequently travels 90 minutes to receive health care, resulting in both loss of work time and high medical bills. Further, her symptoms have impacted her family and her ability to meaningfully engage with her young daughter.

Ms. Maughan cited recent estimates of nearly 18 million Americans living with Long COVID. Their stories highlight numerous individuals and their families that face the challenges of living with the debilitating symptoms of Long COVID, as well as the resulting financial burden. Moreover, she commented that she and all individuals affected by Long COVID implore researchers and policymakers to consider patients' perspectives and to include patients in relevant discussions whenever possible, noting individuals affected by Long COVID want meaningful research in a timely manner and treatments based on real-world evidence research.

Angela Meriquez Vazquez

Ms. Vazquez shared that she developed COVID-19 in March of 2020. Her condition initially began as a mild illness that rapidly progressed to a series of life-threatening symptoms, including blood clots, strokes, brain swelling, seizures, heart palpitations, shortness of breath, confusion, and a progressive loss of sensation in her limbs. While Ms. Vazquez survived the

initial infection, she continues to experience neurologic, immunologic, and metabolic symptoms that affect her daily life.

Ms. Vazquez faced numerous challenges navigating the health care system. Her symptoms, which she described as systemic and debilitating, were initially dismissed by physicians as anxiety. This dismissal, as well as the discrimination she faced, exacerbated her disabilities.

She commented that experiences like hers continue to harm patients. Recent estimates from the U.S. Centers for Disease Control and Prevention (CDC) indicate that Black, Hispanic, and Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, Intersex, Asexual (LGBTQIA+) communities are experiencing the highest prevalence of Long COVID in the United States. Ms. Vazquez also described data indicating people of color (PoC) are prescribed antivirals less frequently than non-PoC. Moreover, she noted that people in rural areas, immigrants, and individuals with low socioeconomic status (SES) may be unable to access adequate health care or engage in clinical trials, leading to worse outcomes among these populations.

Ms. Vazquez emphasized that it is essential for government institutions to invest in research on Long COVID and related IACCs and ensure that: (a) research continues to be supported; (b) findings are disseminated rapidly; and (c) clinical practices can better support patients. She further urged RECOVER-TLC to include people living with Long COVID, as well as people from underrepresented or underserved populations, in clinical trial leadership positions and study designs. Finally, she implored RECOVER-TLC to increase transparency when communicating decision-making processes so that people living with Long COVID are no longer dismissed and to increase community engagement by aggregating, documenting, and disseminating comments from people living with Long COVID.

Liza Fisher

Ms. Fisher shared that after contracting SARS-CoV-2 she was hospitalized for four months, followed by an additional three months of care in a rehabilitation hospital. She now lives with Long COVID and has been diagnosed with multiple IACCs and comorbid conditions (e.g., depression) that affect her everyday life. Ms. Fisher described the need to grieve the life that she thought she was going to live before developing COVID-19 and Long COVID. She commented that her social life has been severely reduced, and her mother had to leave the workforce to support Ms. Fisher as a live-in caregiver.

Ms. Fisher noted the most difficult part of her Long COVID experience is living with the unknown. As little is understood about the breadth of symptoms that people with Long COVID may experience, and even less is known about effective treatment strategies and overall recovery, she identifies herself as a “science experiment.” She noted that many initial research questions about COVID-19 remain unanswered, and further questions regarding Long COVID remain to be explored.

Treatment needs were at the forefront of Ms. Fisher’s presentation. She highlighted numerous treatments pursued by people living with Long COVID, including those that are surgical, pharmacological, and holistic. For example, Ms. Fisher has undergone several surgeries,

including the implantation of a neuromodulator to assist with pain management, and she wears rose-tinted glasses to assist with migraines. She has explored herbal therapies, red light therapy, and numerous pharmaceutical medications. In addition to physical support, she emphasized the importance of receiving mental health treatment, as both the mental weight of the unknown and the persistent physical discomfort of symptoms related to Long COVID impact her mental well-being. Ms. Fisher noted that it is unlikely a single treatment will resolve all Long COVID symptoms; however, the combined experiences of people with Long COVID may inform research practices.

Key Takeaways

People living with Long COVID experience frequent dismissal by physicians and difficulty obtaining diagnoses and adequate treatment opportunities. The three speakers emphasized the impact that Long COVID has on their daily lives, as well as the lives of their loved ones. There is a critical need to include people with lived experiences and underrepresented groups within RECOVER-TLC leadership and as consultants and patients for clinical trials.

Panel Discussion

Patient Experiences

Several Workshop participants agreed with Ms. Fisher's sentiment that the feeling of being a "science experiment" is pervasive among people living with Long COVID. Participants also agreed that experiencing poor physical health can contribute to worsened mental health, necessitating mental health care alongside physical health care. The participants commented that people living with Long COVID may desire to advocate for themselves and contribute to both research and social communities; however, they should prioritize their well-being first and foremost. They also noted that people living with Long COVID can further engage with this community through research opportunities, virtual platforms, or in-person support groups.

Advocacy

Both patients affected by Long COVID and researchers at the Workshop highlighted the following challenges in recruiting patients with Long COVID for clinical trials: (a) patients' concerns of unacknowledged or unidentified Long COVID; (b) politicized issues related to Long COVID; and (c) language barriers that may be present with immigrant communities. Supporting networks of community health workers who can serve as liaisons between the health care system and underserved or underrepresented communities may help overcome these barriers. Patients at the Workshop also described other barriers to clinical trial participation and health care access, including transportation, limited hours for office visits during certain times of day, and an inability to take time off from work to recover from tiring medical procedures.

Patient advocates and other patients with Long COVID at the Workshop urged medical professionals and clinical trial researchers to expand office hours to accommodate visits outside of traditional working hours and to increase access to public transportation via travel routes or reimbursements. A physician at the meeting urged people living with Long COVID to inform research efforts by communally collecting a compendium of their symptoms, treatments that they have sought, and results of those treatments.

Long COVID Definitions and Impact on Clinical Trials

Dr. Jerry Krishnan, University of Illinois at Chicago

As post-SARS-CoV-2 infection symptoms emerged, organizations began developing and disseminating their own terminology to refer to both associated symptoms and the affected patient population. This lack of common terminology contributed to challenges in developing foundational and clinical research, clinical management practices, surveillance methods, and patient care and support services. Recognizing these challenges, the Office of the Assistant Secretary for Health (OASH) and the Administration for Strategic Preparedness and Response (ASPR) in the U.S. Department of Health and Human Services (HHS) directed the National Academies of Sciences, Engineering, and Medicine (NASEM) to develop a consensus definition for the continuation of symptoms following infection with SARS-CoV-2. To support patient engagement, NASEM adopted the term "Long COVID" to describe post-SARS-CoV-2 infection symptoms as it is a simple and familiar term.

The NASEM committee developed the following consensus definition for Long COVID:

> *"Long COVID is an [IACC] that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems."*

This definition is intended to be inclusive of all demographics, and a primary care physician can use it to make a diagnosis. The 3-month time frame allows enough time for a clinician to explore alternative causes for a patient's symptoms. The inclusion of "IACC" highlights the ongoing nature of Long COVID and its association with a triggering infection without implying pathobiological mechanisms. The disease state wording emphasizes the systemic effects of Long COVID and reflects the heterogeneity of experiences for those with Long COVID.

The definition for Long COVID needed to be broad enough to accommodate individual experiences while mitigating the risk of false diagnoses. It took a NASEM-convened Committee of SMEs 18 months to devise the definition, during which time it established the Committee on Examining the Working Definition for Long COVID to review existing definitions of Long COVID; consider previous efforts toward researching and developing treatments for Long COVID; and recommend related technical terms and their applications. The Committee on Examining the Working Definition for Long COVID incorporated feedback from over 1,300 patients, health care professionals, researchers, and other interest groups to ensure that patients' perspectives and interdisciplinary interests were incorporated into the final definition.

The definition will support clinical trials by allowing for study-specific inclusion and exclusion criteria based on patient experiences and establishing support for master protocols while acknowledging diverse patient experiences and clinical treatments.

Panel Discussion
Moderator: Dr. Ian Simon, Department of Health and Human Services (HHS)/ OASH
Panelists: Dr. Jerry Krishnan, University of Illinois at Chicago; Karyn Bishof, COVID-19 Longhauler Advocacy Project; Dr. Sharon Saydah, CDC; Dr. Serena Spudich, Yale University

Impact of a Consensus Long COVID Definition
The development of a consensus definition for Long COVID established a foundation for supporting the development of CDEs, master protocols, and common approaches to identifying and treating patients. The broad definition acknowledges and supports the breadth of symptoms and other experiences of individuals living with Long COVID. Additionally, the consensus definition will enable more effective collaborations among Long COVID researchers, clinicians, and others studying related symptoms, mechanisms, and IACCs in populations with varying underlying conditions.

Identifying biomarkers is of high priority; however, as the consensus definition is broad, researchers must still develop specific study criteria within the definition of Long COVID and design studies with a translational impact in mind. Inclusion and exclusion criteria, as well as phenomena of interest, should be carefully defined to: (a) reflect patient experiences; (b) include measures that can be tested by clinicians; and (c) describe meaningful outcomes for patients.

Research Opportunities
The NASEM Committee acknowledges and encourages the evolution of the consensus definition of Long COVID as new scientific and clinical discoveries are made. Researchers are encouraged to communicate with patients and clinicians to identify phenomena (e.g., symptoms, biomarkers) relevant to patient health care needs. Importantly, the research community should study biomarkers, pathobiology relevant to the clinical diagnoses of Long COVID, symptoms, and variables influencing the development of Long COVID.

Overview of Observational Studies—Implications for Clinical Trial Design

Dr. Leora Horwitz, New York University

Observational data are extremely valuable and should be incorporated in the design of clinical trials focused on Long COVID. Since Long COVID continues to be an emerging condition, patient experiences are essential to inform the disease definition. Data from high quality observational studies will enable precise descriptions of Long COVID across heterogeneous manifestations; inform how often certain disease outcomes occur (e.g., how many people become infected with SARS-CoV-2 and develop Long COVID without preventative measures or recover from COVID-19 without treatment); and support clinical trial design, funding, and enrollment as well as the interpretation of study findings on safety and efficacy of potential prevention and treatment approaches. Observational studies also can identify patient populations particularly impacted by Long COVID, variations across demographics, and biological abnormalities in

patients with Long COVID that may serve as targets for potential therapeutics, which can then be tested for treatment safety and efficacy.

To address existing knowledge gaps, RECOVER observational studies were designed with consistent, repeated measures in the same participants to enable a better understanding of disease outcomes. Long-term, prospective follow-up of study cohorts was conducted to enable rigorous assessment of Long COVID incidence and recovery trajectory. RECOVER's large, representative sample sizes enable subgroup analyses across demographics, with more than 14,000 participants in each of the adult and pediatric cohorts. RECOVER initiatives also include electronic health record (EHR) studies of more than 60 million patients and biospecimen collection for physiologic studies to support the identification of therapeutic targets.

Clinical Data from Observational Studies

Long COVID: Lessons Learned and the Road Ahead
Dr. Ziyad Al-Aly, U.S. Department of Veterans Affairs (VA)/ Washington University in St. Louis

People affected by Long COVID experience viral persistence, immune dysregulation, microbiome dysbiosis, and inflammation, resulting in cardiovascular, neurological, and metabolic symptoms that extensively impact individuals, their communities, and society.

In a 2024 publication, Dr. Al-Aly and colleagues offered several policy considerations to address the Long COVID crisis, including preparedness efforts for future pandemics. Policy efforts may be aided by establishing professional scientific societies for Long COVID, as well as a coordinated interdisciplinary research agenda, which will help build consensus on clinical definitions and endpoints. Other Long COVID research considerations include understanding pathobiological mechanisms, assessing potential diagnostic biomarkers, establishing clinical trials of potential treatments, and delineating the epidemiology and clinical course of Long COVID, as well as examining health care delivery and the economic and societal impacts of Long COVID.

Among the lessons learned from Long COVID efforts is the importance of listening to patients about the differences in their Long COVID experiences, especially when considering ME/CFS and other IACCs. Input about the impacts of Long COVID collected from social media revealed important details about patient experiences. Patients voiced a desire that the condition be treated like a physical illness (e.g., with pharmaceutical interventions), which may be aided by expanding antiviral research and development. Others emphasized the need for safe spaces via masking and air filtration or ventilation. Long COVID study design should prioritize empiricism and establish concrete clinical definitions while also reflecting the complexity of the disease.

Longitudinal Study of COVID-19 Sequelae and Immunity in Adults
Dr. H. Clifford Lane, NIAID

The NIAID Division of Intramural Research is conducting multiple studies, one of which began in Spring 2020 as a long-term follow-up study. This study aimed to assess Long COVID and

enrolled 283 adults with SARS-CoV-2 infection who experienced COVID-19 symptoms for six or more weeks. Additionally, 212 demographically matched control individuals without SARS-CoV-2 infection were included. The study collected longitudinal follow-up data every six months, as well as biospecimen samples. Individuals with COVID-19 were relatively healthier than seen in other studies, with only 10 percent experiencing hospitalization. Throughout the duration of the study, 163 individuals in the control group contracted COVID-19, with one participant developing Long COVID.

Participants in the SARS-CoV-2-infected group reported more symptoms than those in the control group. However, no significant differences in abnormal test results were observed between COVID-19 and control groups, nor were abnormal findings associated with specific symptoms. Additional exploratory studies did not demonstrate evidence of abnormal systemic immune activation or persistent viral infection in participants with Long COVID, and targeted biomarker testing similarly revealed no abnormalities. Furthermore, spike antigen levels in patient plasma, as determined by single molecule array (SIMOA) assays, showed similar distributions between control, patients with COVID-19, and individuals with Long COVID. A key observation of this study, which should be considered when designing future clinical studies, is that COVID-19 symptoms change over time.

The Pediatric COVID Outcomes Study (PECOS)—a collaboration between NIAID and Children's National Hospital—is a longitudinal study evaluating short- and long-term outcomes following SARS-CoV-2 infection in 800 children who recovered from infection as well as 300 uninfected children in the control group. Enrollment in PECOS occurred during the transition between delta and omicron variant prevalence. Pediatric participants infected with SARS-CoV-2 were more likely to report symptoms compared to uninfected children. However, the distribution of symptoms differed from what has been observed in adults, highlighting a discrepancy between clinical manifestations of COVID-19 between adult and pediatric populations.

Panel Discussion

Moderator: Dr. Serena Spudich, Yale University
Panelists: Dr. Leora Horwitz, New York University; Dr. H. Clifford Lane, NIAID; Dr. Ziyad Al-Aly, VA/Washington University in St. Louis; Dr. Igor J. Koralnik, Northwestern University; Dr. Melissa Stockwell, Columbia University; Dr. Helen Ward, Imperial College; Dr. Simon Pollett, Uniformed Services University

Care Models for Patients with Diverse Experiences

Patients' diverse experiences with Long COVID (e.g., symptoms, underlying conditions, quality of life) should be acknowledged and prioritized, and physicians and researchers should advocate for these individuals. Many health care systems, such as the VA Medical Center in Salt Lake City, Utah, address patient needs individually with a team of doctors from various specialty fields and utilize centralized medical records. This approach to patient care can be resource-intensive, and health systems research is needed to support the feasibility of scaling this care model while ensuring its cost-effectiveness. A similar care model has successfully been executed at the Northwestern Medicine Comprehensive COVID-19 Center, which consists of

clinics across 14 different specialties and includes virtual care options. The establishment of this center did not require any financial resources since these clinics already existed and were brought together to provide comprehensive COVID-19-specific patient care.

Long COVID Recovery

Recovery rates from Long COVID vary by population as well as by the definition of "recovery." While some physicians believe a patient is not recovered if symptoms persist, others consider recovery from Long COVID as an improvement of COVID-19-associated symptoms that have persisted for longer than three months. One long COVID patient at the Workshop emphasized that, although her symptoms have improved over the past two years, she has not regained the full health she had prior to COVID-19. Additionally, recovery-focused studies have provided mixed results that demonstrate the possibility of recovery from Long COVID, even if full recovery has not yet been more widely observed. In some studies, Long COVID patients have reported decreased symptom burden, increased quality of life, and improved performance in online cognitive assessments. However, other studies indicate that full recovery from Long COVID occurs in less than 10 percent of cases and, even when patients show partial improvement, which typically occurs within the first 12 months following Long COVID development, many still experience residual symptoms and infections.

Long COVID in Pediatric Populations

Pediatric Long COVID exists, and research involving pediatric patients should be performed in addition to adult studies. Current Long COVID studies in pediatric cohorts (e.g., PECOS, RECOVER Pediatric Observational Cohort Study [RECOVER-Pediatrics]) have highlighted differences in symptoms between pediatric and adult populations, especially for school-age children and younger. These studies have informed the identification of key phenotypes that could be useful in pediatric clinical trials on Long COVID. Data from the RECOVER-Pediatrics observational study identified four Long COVID subtypes in school-age children and three subtypes in adolescents (with ongoing investigation in children less than 5 years old), demonstrating heterogeneity of Long COVID experiences even within the same age groups. Pediatric experts at the Workshop recommended including children of all ages, even from the beginning of life, in clinical trials to ensure robust data on symptom trajectory and outcomes.

One major challenge in performing pediatric studies is that very few children are being diagnosed with Long COVID. Since no definition for pediatric Long COVID currently exists, pediatricians do not always know how to diagnose it. To address this challenge, RECOVER-Pediatrics will train pediatricians to recognize Long COVID. Additionally, using EHR data from pediatric patients, researchers are working to develop computable phenotypes for improving Long COVID diagnosis in these populations.

Clinical Trial Participant Inclusion

To identify the most effective interventions for Long COVID, clinical studies should include participants representing a variety of Long COVID subtypes or intervening exposures that can lead to heterogenous Long COVID manifestations. It is important to note that designing trials which require in-person specialist clinic visits or a documented Long COVID diagnosis may

exclude segments of populations with Long COVID that could provide valuable insight into potential risk factors of disease. Researchers should also collect and analyze data from EHRs and from patient cohorts within and outside of RECOVER to inform the differentiation and prediction of Long COVID subtypes and to understand indicators of remission and relapse. Identifying appropriate control groups, potentially using pre-COVID-19 health care data, will also reinforce the validity of clinical trial results. Workshop participants emphasized the importance that reports about these clinical trials should accurately reflect patient experiences.

To ensure the involvement of study participants from rural areas and other vulnerable populations, RECOVER trials have offered accommodations—such as transportation, visits outside of school or work hours, and in-home visits—to families of pediatric participants. Additionally, study personnel drive mobile vans to meet study participants where they live, and trial participants who travel more than 150 miles have been reimbursed for an overnight stay. Additionally, RECOVER leveraged the Long COVID Care Network funded through the Agency for Healthcare Research and Quality (AHRQ), a network with sites in multiple rural communities. These efforts resulted in a 5 percent rural enrollment rate out of total study participants; although less than the proportion of the national rural population, this percentage of rural study participants is higher than in many other studies. Future research efforts should also consider using telemedicine to expand participation from individuals with Long COVID in rural areas.

Leveraging Existing Resources for RECOVER Clinical Trials

RECOVER-TLC can leverage existing data sources to bolster its multipronged analytical and observational approach. The RECOVER Biospecimen Repository contains hundreds of thousands of biospecimens that can be used for extensive laboratory analysis and clinical assessments. Cohort participants that provided these specimens are being followed over time, and surveys are being administered to these individuals regarding changes in symptoms or quality of life. A similar repository exists for biosamples that have been collected from babies congenitally exposed to SARS-CoV-2. These individuals will also be followed longitudinally to assess the effects of viral exposure on growth and development.

Data collection in health care systems within the United States also may prove valuable to RECOVER efforts. The Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study enrolled a large cohort of military health system (MHS) participants, which enables researchers to observe functional endpoints through fitness tests for military duty and leverage biosamples collected pre-COVID-19 for biomarker development. Researchers also used machine learning to systematically analyze different phenotypes associated with patient-reported outcomes (PROs), and the results replicated those from RECOVER study machine learning analyses. Additionally, the U.K. Real-time Assessment of Community Transmission (REACT) study collected longitudinal data from 3.2 million people who were 5 years old and older. Researchers can leverage these data to assess Long COVID disease trajectories with or without vaccination and estimate disease impacts that may encourage industry investment in Long COVID clinical trials.

Researchers also may identify details about Long COVID from communities experiencing non-COVID-19 IACCs (e.g., ME/CSF). Knowledge obtained through these experiences and research efforts is crucial to understanding Long COVID in the broader context of IACCs. RECOVER has incorporated a series of questions related to these conditions to better capture other viral-associated illnesses in the medical histories of study participants.

Pathobiology Studies—What is Known, What Information is Needed, What are the Challenges to Providing the Basis for Future Clinical Trials

Neuroinflammation, Vascular Disease Measures, and Innate Immune Activation in Long COVID

Dr. Mike VanElzakker, Harvard University

Long COVID patients can experience neuroinflammation that may lead to vascular disease. In a 2024 study, positron emission tomography (PET) scans were conducted in 12 participants with Long COVID onset prior to August 2021 who exhibited common neuropsychiatric symptoms and at least one symptom from each of the ME/CFS International Consensus Criteria clusters. The levels of translocator proteins, which are neuroinflammation markers released by microglia upon activation by pathogen-associated molecular patterns such as the SARS-CoV-2 spike protein, were assessed and observations found that scans of individuals with Long COVID showed heterogeneous translocator protein activation when compared to pre-COVID-19 control PET scans. Notably, translocator protein levels were consistently elevated in brain regions that contribute to symptoms such as fatigue and difficulty concentrating. Translocator protein activation was observed at the boundary of the ventricles around the corpus callosum and within densely vascularized regions, such as the posterior midcingulate, suggesting that the vasculature may be affected by neuroinflammation in Long COVID participants. Analysis of blood samples for markers of vascular damage identified seven biomarkers, including fibrinogen and L-selectin, that correlated with neuroinflammation as determined by translocator protein PET signals; however, no correlation was noted between vascular damage markers and standard markers of inflammation (e.g., c-reactive protein (CRP), proinflammatory cytokines), further highlighting the specificity of COVID-19-related neuroinflammation for inducing vascular damage.

Viral persistence also may play a role in these inflammatory responses. Recent data revealed that Long COVID patients show fibrin-amyloid microclot formation and increased pathogen-induced neutrophil activation that correlates with markers of platelet activation. SARS-CoV-2 spike protein presence also triggers conversion of fibrinogen to fibrin, with neuroinflammation blocked by preventing spike protein interactions with complement receptor 3 found on neutrophils. These data suggest a potential neuroinflammation cascade in Long COVID in which spike protein drives fibrin(ogen) activation and triggers an innate immune response that includes neutrophil activation via complement receptor 3. Activated neutrophils then travel to the blood-brain barrier to activate microglia, which release translocator proteins and other neuroinflammation molecules that cause sickness-related symptoms.

Endothelial Injury, Thrombosis, Complement Activation
Dr. Resia Pretorius, Stellenbosch University

Studies have found abnormal clotting and vascular damage, such as endothelialitis, in Long COVID patients. These associations may be due to viral persistence that maintains circulating spike protein levels and causes dysregulation of inflammatory molecules. These inflammatory molecules, as well as the spike protein, can bind fibrinogen proteins, resulting in the formation of fibrinogen amyloid microclots that can drive inflammation and neuropathology in COVID-19. Other studies have shown that circulating inflammatory molecules and immune cells, such as neutrophil extracellular traps (NETs), are structurally associated with these microclots in COVID-19 patients.

Prior research indicates that amyloid microclots found in platelet-poor plasma may be an important diagnostic biomarker for Long COVID and may facilitate identification of subtypes that involve thrombotic complications. Although these microclots have the composition of "true" blood clots (i.e., they consist of platelets, fibrin, red and white blood cells, NETs, and other plasma proteins), they are fibrinolytic-resistant, which decreases the suitability of the fibrin degradation protein fragment D-dimer as a biomarker. Microclot profiles in patients with Long COVID, including microclot size, number, and biochemical characteristics, may be more informative as diagnostic indicators in Long COVID studies, especially because microclot presentation differs among viral variants or infection time periods. A recent study detailed an effective microclot flow cytometry method to quantify microclots from plasma samples.

SARS-CoV-2 Persistence as a Target for Long COVID Trials
Dr. Michael Peluso, University of California San Francisco (UCSF)

Pathogen persistence is a complication of many IACCs as well as COVID-19, with studies showing that SARS-CoV-2 RNA persists up to two years post-viral infection, residing in regions with immune cell infiltrates. These studies further revealed the presence of double stranded RNA, which suggested that the viral life cycle is still occurring. This persistence may be maintained by many viral and host cell factors and influenced by acute SARS-CoV-2 infections. Supporting this hypothesis, studies have found that maximum viral load and polymerase chain reaction (PCR) positivity duration throughout the first three weeks after an acute SARS-CoV-2 infection predicted the presence of Long COVID symptoms in the following three to five months. Mechanisms of viral persistence in Long COVID remain unclear, as do approaches for prevention, measurement, and treatment.

Although some studies suggest that viral persistence has the potential to cause Long COVID, most of these studies were small in size and had short follow-up periods. Ongoing studies exploring viral persistence are often complicated by SARS-CoV-2 infections that occur in control participants. Future studies should increase inclusion of fully recovered SARS-CoV-2 participants and deliberately selected COVID-19 phenotypes to draw stronger mechanistic conclusions. In addition, studies with large enrollment numbers may be informed by simultaneously conducting multiple small, focused trials that share eligibility criteria, measurements, and endpoints while targeting viral persistence with different therapeutics. Future studies should

also focus on identifying biomarkers to assess contributions of viral persistence to Long COVID. Researchers can bolster biomarker development by increasing assay sensitivity, assessing phenotypic variability within participants over time, and expanding the capacity to examine tissue-based markers.

Biorepositories and Candidate Biomarkers by Pathway: Viral, Inflammatory, and Immunologic
Dr. Paul J. Utz, Stanford University

Previous RECOVER biomarker studies have incorporated biospecimen collection and analysis, which can help accelerate identification of biomarkers for use in RECOVER-TLC studies. The RECOVER team collected both whole blood for sequencing and other specimens (e.g., stool, urine, saliva) at multiple time points ranging from three months to four years post-baseline collection. RECOVER also collects both pre-pandemic and pre-infection samples, as well as samples from healthy, uninfected control participants who become infected with SARS-CoV-2. Any uninfected participants who become infected are re-enrolled as infected controls, which restarts the timeline of biospecimen collection. As of May 27, 2024, approximately one million specimens have been logged into the RECOVER Biospecimen Inventory across adult, pediatric, and autopsy cohorts.

In addition to incorporating RECOVER biomarker analyses, future RECOVER-TLC trials should incorporate several additional analyses currently being assessed in the Selective Trial of Paxlovid for Postacute Sequelae of SARS-CoV-2 Infection (STOP-PASC) study. STOP-PASC data suggest that autoimmunity may play a role in pathogenesis, despite the unlikelihood of autoantigens driving this response. Thus, RECOVER-TLC trials should measure auto- and viral-associated antibody levels using appropriate existing techniques, with the understanding that intravenous immunoglobulin (IVIG) may confound results. In additional, RECOVER trials should conduct Trans-Omics for Precision Medicine (TOPMed) analyses, such as DNA whole-genome sequencing, RNA sequencing, and O-link proteomics, as well as analyses of peripheral blood mononuclear cells (PBMCs). Important considerations for these approaches include collection method (e.g., true culture system whole-blood collection), processing time and location (e.g., local vs. central processing), matching and batch effects (e.g., running all longitudinal samples from the same participant simultaneously), and appropriate assay types (e.g., descriptive or functional assays).

Panel Discussion
Moderator: Dr. Joseph Breen, NIAID
Panelists: Dr. Mike VanElzakker, Harvard; Dr. Resia Pretorius, Stellenbosch University; Dr. Michael Peluso, UCSF; Dr. Paul J. Utz, Stanford University; Dr. Amy Proal, PolyBio Research Foundation

Establishing Relevant Long COVID Biomarkers
Biomarkers identified from prior studies may not accurately reflect Long COVID status. First, studies that did not solely enroll control participants with no COVID-19 history cannot distinguish Long COVID-specific biomarkers from those related to acute COVID-19. Furthermore, symptom resolution after SARS-CoV-2 exposure does not necessarily mean

restoration of health status prior to infection; viral infection may reset baseline inflammation levels, even for individuals whose symptoms resolve. Conducting focused experimental clinical studies that assess numerous biological parameters may resolve the issues seen with prior studies and be more effective at identifying relevant biomarkers. Researchers could use results from these small studies to identify specific biomarkers in subtypes of Long COVID that reveal patient populations of interest, as well as inform the design of large studies that incorporate multiple biomarker panels in a greater number of participants. These large studies should utilize the RECOVER Biospecimen Repository and similar non-RECOVER resources, such as pre-COVID-19 NIH-banked samples. Collaborations across research groups will help make these approaches to both large and small studies possible.

Addressing Neuroinflammation in Long COVID Patients

Many patients experiencing Long COVID-associated cognitive dysfunction and fatigue have been misdiagnosed with functional neurological disorder (FND) by providers who may not acknowledge the contributions of Long COVID to these conditions. A FND diagnosis may not appropriately address aspects of a patient's symptoms that are related to Long COVID, and providers should only diagnose patients with FND when they observe multiple positive signs associated with this condition, not just when a patient exhibits neuroinflammation. The Long COVID research community may help expand educational infrastructure through patient advocacy and data collection efforts, including RECOVER and the U.S. Agency for Healthcare Research and Quality (AHRQ) programs, to better inform clinicians about the neuroinflammatory contributions of Long COVID.

Treatment of Long COVID Symptoms with Developed Therapeutics

Researchers should consider leveraging FDA-approved drugs as treatments for Long COVID patients. For example, combinations of anticoagulant and antiplatelet medications could address COVID-19-associated microclots. Multiple countries are currently testing combinations of these therapies, including a U.K. study that will also assess the ability for molecules, such as nattokinase and serrapeptase, to break down microclots. However, safety data are still necessary to authorize extended administration of any FDA-approved drugs.

Monoclonal antibody interventions may also be a viable treatment approach for adult Long COVID patients. Since companies previously developed and manufactured monoclonal antibodies following the alpha wave of SARS-CoV-2, they could promptly test the therapeutic potential of these antibodies, possibly as part of combination trials.

What Can Be Learned from Other Related Syndromes to Inform the Design of Long COVID Clinical Trials

Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome that Inform the Design of Long COVID Clinical Trials

Dr. Avi Nath, NINDS

Many challenges hinder the design and success of clinical trials focused on COVID-19 treatments. Multiple placebo-controlled studies of treatments—including Paxlovid, stem cell therapy, and antibodies neutralizing human endogenous retrovirus-W—have failed to produce an effective Long COVID treatment. Another study assessing checkpoint inhibitors caused increased negative health outcomes. Furthermore, confounding results from studies are, in part, due to the existence of various symptoms of Long COVID and other IACCs, including ME/CFS, that phenotypically overlap with one another. However, a study of a post-infection ME/CFS patient cohort demonstrated the possibility of designing effective trials for ME/CFS and Long COVID. Although only 17 participants were selected out of 500 recruited for the study, investigators conducted extensive phenotyping analyses in this homogenous cohort that revealed novel antigen persistence contributions in these participants. This antigen persistence decreased the ability of B cells to switch from IgM to IgG, which led to improper activation of the innate immune system that caused neuroimmune dysfunction and ultimately resulted in an ME/CFS phenotype. Immune system profiles showed similar dysregulations in Long COVID patients that persisted up to one year following SARS-CoV-2 infection.

Other Long COVID clinical trials are in progress currently. Participant enrollment for a study investigating IVIG in Long COVID is ongoing, and an institutional review board (IRB) has been approved for a study investigating viral reservoirs in Long COVID. Additionally, a study focused on checkpoint inhibitors in Long COVID is in development, although there is no funding currently available for this project, and increased negative health outcomes resulting from previous checkpoint inhibitor trials necessitate extensive scientific committee review. When designing future trials for Long COVID and ME/CFS, researchers should define PEM and create a clinical scale to help develop clinical outcome measures. Additionally, investigators should stratify study participants based on their primary immune dysfunction to better assess immunological phenotypes, such as B cell activation, T cell exhaustion, and innate immune system activation. Researchers also should consider innovative clinical trial designs that involve platform studies and placebo-controlled crossover studies to simultaneously assess multiple therapeutic candidates.

Postural Orthostatic Tachycardia Syndrome

Dr. Peter Rowe, Johns Hopkins University

POTS, a form of orthostatic intolerance that is more frequently present in children, has been difficult to treat in clinical trials, in large part because mechanistic heterogeneity of the disorder often complicates outcome measurements. POTS disrupts proper physiology, by significantly increasing patient supine-to-standing heart rate elevation in the morning when compared to

the afternoon. POTS also is associated with several comorbidities that can impact signal detection of therapies, so studies testing treatments for specific POTS-related comorbidities should limit enrollment to patients exhibiting comorbidities of interest rather than including all POTS patients.

Two trials have produced results that implement considerations of POTS-related heterogeneity. First, Taub et al. (2021) outlined a month-long crossover study that required eligible patients to have a POTS diagnosis with head-up tilt norepinephrine levels of 600 pg/mL or higher. Administering ivabradine to these participants decreased heart rate elevation and improved quality of life. Vernino et al. (2024) recruited POTS patients with more severe autonomic symptoms as determined by a Composite Autonomic Symptom Score-31 (COMPASS-31) of 40 or higher in combination with at least three of five autoimmune POTS-related conditions. This 12-week double-blind study showed that IVIG treatment improved COMPASS-31 scores about three times as often compared to control, treated patients. This difference was not statistically significant, and the study did not demonstrate many clinical differences typically associated with IVIG treatment. This lack of clinical differences may have been due to small study sample size, favorable response from placebo-administered individuals that decreased the difference between treated and control groups, and the reduced probability of response as a result of prolonged disease duration and severity of symptoms.

To effectively address other forms of orthostatic intolerance, ME/CFS, and Long COVID, clinical trial strategies should utilize results from N-of-1 studies, as well as stratification of patients into different subsets to address duration and severity of illness. Studies focused on pediatric populations may also be useful because this cohort is less heterogeneous than adult cohorts. Other potential study design approaches can include run-in active treatment periods to address symptoms related to comorbid disorders and randomized withdrawal of medications during a trial. Study design teams should also consider shorter trial durations and observational analyses that assess how treatments impact previous IACC-related damage compared to ongoing damage in patients.

Lessons Learned in a Pediatric Pandemic Research Network—Multisystem Inflammatory Syndrome in Children

Dr. Adrienne Randolph, Harvard University

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe pediatric condition in which individuals under 21 years old with recent or current SARS-CoV-2 infection experience fever, exhibit laboratory evidence of inflammation, and demonstrate clinically severe illness with multisystem involvement and no other plausible diagnoses. Investigators of the Overcoming COVID-19 network established a real-time public health surveillance registry of pediatric patients admitted to the hospital with SARS-CoV-2 complications. The network clinically characterized MIS-C in an immunobiology study of 800 hospitalized patients. Analysis of these data revealed that MIS-C is a post-infectious syndrome that emerges between 2–6 weeks after a COVID peak in each geographical location and disproportionately affects children between the ages of 5 and 14 years, especially those of racial and ethnic minority populations.

In addition, clinical outcomes were generally favorable; patients improved with treatments of IVIG, steroids, and other anti-inflammatory mediators, and mortality rates were low. Although clinicians were initially concerned about Kawasaki disease-like cardiovascular complications in patients with MIS-C, most of these symptoms quickly resolved following treatment.

Many ongoing studies are addressing the molecular mechanisms of MIS-C that determine clinical outcomes. Whole genome sequencing of MIS-C patients revealed several genetic variants that explain susceptibility to this condition, most of which are heterozygous or hemizygous variants in host immunity-related genes. In addition, phage immunoprecipitation sequencing (PhIP-seq) analyses identified elevated levels of autoantibodies for three proteins of interest, most notably intracellular antigen sorting nexin 8 (SNX8). Results from a subsequent study recapitulated SNX8 autoantibody binding to T-cell receptors in CD8 cells collected from MIS-C patients, suggesting a role for molecular mimicry as an enigmatic form of immune dysregulation in Long COVID. Ongoing experiments also have revealed a higher frequency of neutrophil NETs, which contain autoantigens, in MIS-C patients compared to those with acute COVID-19. Additional evidence is needed to distinguish whether NETs directly contribute to MIS-C phenotypes or simply serve as a marker of tissue damage.

Panel Discussion

Moderator: Dr. H. Clifford Lane, NIAID
Panelists: Hannah Davis, Patient-Led Research Collaborative; Jaime Seltzer, MEAction Network; Dr. Alba Azola, Johns Hopkins University; Dr. Ian Lipkin, Columbia University; Dr. Steve Deeks, UCSF

Leveraging IACCs to Advance Research in Long COVID

Although ME/CFS research may not address all manifestations of Long COVID, it may provide valuable information that researchers can leverage to understand related aspects of Long COVID, such as phenotypic heterogeneity, innate immune responses, and the burden of symptoms (e.g., brain fog, exercise intolerance, cerebral hyperperfusion syndrome). Other aspects of previous ME/CFS studies can help inform the design of clinical trials that incorporate validated tools that assess quality of life, fatigue, and functional capacity; illness duration and severity; endpoints and clinical outcome; and biomarkers of relapse. Since research on ME/CFS tends to be logistically challenging, patient perspectives have provided significant insights about the condition. Despite Long COVID often triggering ME/CFS onset, researchers should consider that ME/CFS can manifest regardless of SARS-CoV-2 infection. Thus, researchers should design Long COVID studies enrolling individuals who developed ME/CFS prior to the pandemic to ensure consistency of ME/CFS-related data from both pre- and post-pandemic ME/CFS patients. The inclusion of both ME/CFS patient groups in Long COVID research may, in turn, identify currently unknown aspects of ME/CFS.

IACC pathology may result from original pathogen-caused damage, viral reactivation, or immunological stressor-induced physiological functional shifts. PEM, a symptomatic consequence of IACCs, is associated with a unique pathophysiological state that often develops after Long COVID onset and results in severe tissue damage and skeletal necrosis. Thus,

RECOVER studies focusing on unique aspects of PEM may provide mechanistic insights for Long COVID and other similar clinical manifestations of related IACCs. Researchers should design PEM studies that assess functional capacity and other validated fatigue measures of participants at a time point following extensive cognitive testing. These assessments can be simple yet effective methods of collecting comprehensive data about both baseline and responsive PEM characteristics.

Industry Engagement in Long COVID Clinical Trials

Industry engagement in Long COVID clinical trials is critical to developing and manufacturing medications for treating Long COVID. Engagement from industry has been limited, in part because prior Long COVID studies were costly and yielded inconclusive results. To make Long COVID research an attractive investment opportunity, researchers outside of industry should design experimental medicine and proof-of-concept studies that identify distinct therapeutic targets based on clinically relevant endpoint results. These approaches have been successful in both HIV and acute COVID-19 drug development. Drug development companies remain interested in developing antiviral therapies that address viral persistence, either through antiviral pharmacological agents (e.g., Paxlovid), immunological interventions (e.g., monoclonal antibodies), or combination approaches.

Public Comment Period

Dr. John Haughton

Dr. Haughton, Medical Director for Renegade Research in the Remission Biome program, commented that many symptoms he now attributes to Long COVID resolved after starting metformin. He characterized Long COVID as a small vessel disease that results in local hypoxia and spike-induced inflammation, particularly of white blood cells in endothelial cell walls. To reverse these effects, Dr. Haughton suggested several pharmacological agents: metformin or naltrexone, which modulate spike activation of toll-like receptor 4; nattokinases and similar proteases, which break down microclots to increase capillary flow; antihistamines, which prevent MAST cell activation; and probiotics, which rebalance gut microbiota away from inflammatory contents.

Dr. Christine Koterba

Dr. Koterba, a pediatric neuropsychologist at Nationwide Children's Hospital in Columbus, Ohio, has worked and conducted research with children experiencing severe COVID-19, MIS-C, and other persistent symptoms following mild COVID-19 cases. She initially believed that Long COVID was largely psychosomatic (i.e., triggered by infection and maintained by psychological symptoms); however, through interactions with patients, families, and patient advocates, her observations of real-life impacts, and reading Long COVID-related literature, she learned that many more factors are responsible for triggering and maintaining Long COVID. While most children recover well following COVID-19, a subset of children experience persistent, if heterogeneous, symptoms that significantly impact their quality of life. She commented that those involved in the care and education of children with Long COVID do not know how to best support them in daily living. Although recognition of pediatric Long COVID has increased, more

work is needed to address best practices of patient treatment and support, as well as prevention of this condition.

Dr. Najla Ba Sharahil

Dr. Najla Ba Sharahil, a Long COVID patient and former pediatric pulmonary fellow at University of Wisconsin-Madison, commented that she saw pediatric patients during the pandemic who experienced significant changes in their quality of life. She shared that she developed Long COVID herself in 2022, which she initially thought was a psychosomatic condition due to stress related to moving to the United States and her training. Dr. Ba Sharahil was diagnosed with MACS followed by POTS, which severely impaired her clinical training and eventually resulted in her resignation before she transitioned to research. She noted that her own experiences, as well as those of many Long COVID patients, show that they are surviving with the condition rather than thriving, often because their physical status and ability to complete tasks change daily. Dr. Ba Sharahil hopes that research can transition toward treating individuals experiencing Long COVID to improve their quality of life.

Josh Porter

Mr. Porter shared that he has lived with Long COVID for approximately 2.5 years. Prior to contracting SARS-COV-2, he had never experienced a major health issue and trained for competitive endurance events. He maintained an overall healthy lifestyle and received all relevant SARS-CoV-2 vaccines and boosters. However, Mr. Porter developed Long COVID rapidly after testing positive for SARS-CoV-2 in May 2022, initially experiencing mild upper respiratory symptoms before developing more intense symptoms, such as intense weakness and fatigue, lightheadedness, significant heart rate variability, and a burning headache that he likened to eating too much wasabi. He is still experiencing these symptoms to this day; their severity and duration varies, but they are all often triggered by excessive physical activity. Although he has given up most of his previous hobbies, Mr. Porter considers himself lucky that he can still work and travel, and he has found new, less physical hobbies.

Mr. Porter expressed frustration about the lack of Long COVID awareness, within both the medical community and the general public. During summer 2024, his primary care provider told him that he was not eligible for certain specialist care because his lab results did not indicate Long COVID illness. He also recognized that many Long COVID patients experiencing worse outcomes and care than himself do not receive appropriate care. Mr. Porter decided to share his story to help improve Long COVID awareness, and he has also enrolled in the ongoing UCSF Long-term Impact of Infection with Novel Coronavirus (LIINC) trial. He hopes that collective research efforts will help provide more effective Long COVID treatments.

Dr. Svetlana Blitshteyn

Dr. Blitshteyn, a urologist clinician and scientist specializing in autonomic disorders including Long COVID, commented that she also serves as the director of the Dysautonomia Clinic in Buffalo, New York. Since the beginning of the pandemic, she has evaluated hundreds of Long COVID patients who are suffering from symptoms such as fatigue, cognitive impairment, dizziness, and exercise intolerance. She noted that at least 70 percent of these patients exhibit

autonomic dysfunction and at least 50 percent exhibit ME/CFS. Dr. Blitshteyn commented that she was the first to characterize 20 patients diagnosed with post-COVID-19 POTS as part of a Long COVID study in which her patients participated. She expressed optimism about the increasing respect for and acknowledgement of patients and their experiences. She expressed her desire to end the dismissive culture in which health care professionals attribute Long COVID-associated physical illness solely to psychological causes.

Dr. Blitshteyn stated that Long COVID patients who are experiencing the greatest symptom burden do not improve from diet and exercise alone, but they often benefit from pharmacotherapies. She has used medications to treat existing patient conditions, including POTS, migraines, neuropathic pain, and insomnia, but she would like to see more therapeutic options as a clinician. She noted that there are no FDA-approved medications specifically for Long COVID. She suggested that creating an accelerated pathway to rapidly repurpose medications, developing additional therapies, and increasing health insurance coverage of such therapies will help clinicians more effectively treat their Long COVID patients.

AW

AW is a Long COVID patient who has contracted SARS-CoV-2 three times. The first infection led to the development of autoimmune disorders and other serious health issues that have increased in severity with each subsequent infection. Over the past two years, AW has experienced suicidality and a significant decrease in quality of life due to loss of a job, marriage, health insurance, savings, and ability to exercise, all due to Long COVID. AW noted that they struggle to complete basic tasks, such as eating and drinking, bathing, and housework. AW also endures daily severe nausea and vomiting due to gastroparesis, slow gut motility, and methane predominant small intestinal bacterial overgrowth. Nutritional deficiencies in thiamine, fatty acids, vitamin D, magnesium, and potassium have likely both contributed to and resulted from Long COVID development. As a result of their experience, AW encourages future RECOVER studies to assess nutritional status of study participants and to test individuals for relevant nutritional deficiencies. AW also noted that their enrollment in a RECOVER study at the University of Arizona site has provided helpful information about understanding and interpreting the health impacts of Long COVID.

Jermaine Greaves

Mr. Greaves is the founder of Black Disabled Lives Matter. He shared that he was born with cerebral palsy and developed Long COVID, which led to the onset of hydrolysis suppurativa. Amid these health challenges, he has been a constant advocate for disability and patient rights in hospitals. Mr. Greaves asserted that the systems of health care and disability have caused people with Long COVID, including himself, to feel like they do not exist. He has felt unheard by physicians and inadequately cared for by his health insurance. Mr. Greaves expressed his desire to be treated like a human being and noted that his experience at the New York University hospital was the first time he felt seen as a patient. He hopes that more physicians become educated on Long COVID and better support individuals suffering from the condition.

Rivka Solomon
Ms. Solomon is a Long COVID patient who also experiences other chronic illnesses that require her to be at or near her bed. When she was 21, she developed mononucleosis and entered semi-remission one year later before developing a second infection of pneumonia, resulting in a ME/CFS diagnosis. She shared that she developed a presumed case of COVID-19 at the beginning of the pandemic before testing was widely available and experienced a burning sensation in her stomach, as well as increased weakness and sickness that led to her being diagnosed with long COVID.

Ms. Solomon noted that ME/CFS lacks significant research funding and that there are no FDA-approved medications for this condition. She also noted that millions of other people with preexisting IACCs also experienced an increase in symptom severity following COVID-19. Due to low research funding, these individuals remain unsure if they have Long COVID, if their original conditions became worse, or both. She is encouraged by the emergence of IACC community advocates who are working to establish a new NIH office dedicated to IACC research. This office could enable coordinated and cost-effective research on these conditions, which will benefit IACC communities, especially because many IACCs have overlapping comorbidities.

Dr. Sevda Sarikaya
Dr. Sarikaya is a neurologist and the mother of a teenager with Long COVID who became bedbound after a mild COVID-19 case. She shared that her daughter has extremely debilitating symptoms that have turned her life into what her daughter describes as “constant turmoil” over the past two years. Both Dr. Sarikaya and her spouse are physicians and have tried several treatments to address the nearly-100 focal seizures her daughter had per day due to Long COVID. The treatments included invasive procedures, like plasmapheresis and IVIG treatments, as well as anti-epileptic drugs. Her daughter also tested positive for human betaherpesvirus 7 in her cerebrospinal fluid, but Dr. Sarikaya’s colleagues told her that antiviral treatments would not be effective for it because her daughter was neither immunocompromised nor positive for other viruses. However, based on anecdotal reports, Dr. Sarikaya decided to administer an off-label oral antiviral medication to her daughter, which eliminated the seizures.

Dr. Sarikaya suggested that, based on her daughter’s experiences, children and adolescents may be immunocompromised by COVID-19. She also voiced the need for Long COVID awareness within the medical community, especially by providing physicians with a basic knowledge of Long COVID and new treatment opportunities to minimize patient harm. She highlighted the sensitivity of children and adolescents to various medications and encouraged researchers to listen to parents and patients when designing studies that assess potential treatments.

Ezra Spier
Mr. Spier developed COVID-19 in September 2022, which led to the onset of chronic symptoms within a week of infection. He noted many ways that his life changed because of Long COVID: he cannot maintain a career due to impacts of his cognitive dysfunction; he has spent most of his savings on medical bills; he cannot engage in social situations without triggering PEM; he

feels he could not adequately raise and care for children because he is unable to take care of his own needs; he does not receive support from his family because all of his siblings have developed Long COVID and cannot provide support; he has not received adequate treatment from health care professionals; and he believes society is unwilling to take basic steps to protect his health from further decline. Mr. Spier voiced his continued support for the Long COVID patient community, and he believes that collaborative efforts are essential to addressing Long COVID. He urged NIH to establish a new office to coordinate research on IACCs and to use their national and global presence to expand Long COVID awareness, research efforts, and therapeutic development.

Leveraging Clinical Trials Already Underway or Planned

Overview of RECOVER Clinical Trials
Dr. Kanecia Zimmerman, Duke University

NIH established the RECOVER Initiative to identify treatment strategies for Long COVID by investigating priority symptom clusters and their causes by evaluating potential therapeutic interventions across domains (e.g., drugs, devices, rehabilitation) to address the underlying causes and symptoms of Long COVID. Protocol development teams consisting of clinical and scientific experts, as well as patients and patient advocates, were guided by principles that involve:

- Prioritizing representation across patient experiences (e.g., including demographically diverse participants with varying COVID subtypes, nonacademic medical center sites);
- Harmonizing across protocols (e.g., time-stamped biospecimen collection; centralized IRBs, data management, and site management and monitoring);
- Building collaborative education and networking (e.g., incorporating 243 principal investigators and 405 co-investigators across 19 specialties, collaboratively generating and disseminating manuscripts, building consensus for future approaches);
- Incorporating pragmatism (e.g., holding monthly meetings and ad hoc troubleshooting meetings, involving sites and study teams with protocol familiarity and established local relationships);
- Investing in infrastructure to enable the rapid inclusion of additional interventions; and
- Building on past experience, including ACTIV.

RECOVER efforts are divided among five primary clinical trial platforms—NEURO, VITAL, AUTONOMIC, SLEEP, and ENERGIZE—across 157 individual sites, many of which participate in multiple platforms. The platform specialties are as follows:

- RECOVER-NEURO assesses cognitive dysfunction through combinations of online patient training programs (e.g., BrainHQ and postacute sequelae of SARS-CoV-2 infection [PASC]-CoRE) as well as through transcranial direct current stimulation via a wearable device.

- RECOVER-VITAL addresses viral persistence, inflammation, and disordered coagulation by determining the effectiveness of different Paxlovid treatment conditions in improving both exercise intolerance and autonomic and cognitive dysfunctions.
- RECOVER-AUTONOMIC, which focuses on individuals with POTS, is testing IVIG, ivabradine, and coordinator-led, nonpharmacological interventions to improve related symptoms.
- RECOVER-SLEEP assesses medications and light therapy to regulate sleep-wake patterns in individuals experiencing hypersomnia or insomnia.
- RECOVER-ENERGIZE determines the efficacy of both personalized cardiopulmonary rehabilitation and structured pacing to address exercise intolerance and PEM.

NEURO and VITAL completed study participant enrollment during summer 2024, while AUTONOMIC, SLEEP, and ENERGIZE are currently enrolling study participants. Each platform has provided valuable insight into effective Long COVID clinical trial approaches (e.g., financial resources required to perform biospecimen analyses) and will provide important new data which can benefit Long COVID patients and prevent viral rebound posttreatment. Future RECOVER efforts may also expand established sites to assess markers of infection.

STOP-PASC and Other Long COVID Trials—Landscape Overview
Dr. Upinder Singh, University of Iowa

Biospecimen samples from immunocompromised and autopsied Long COVID patients have previously revealed viral persistence, implicating this phenomenon as a potential cause of Long COVID. Contributions of viral persistence to Long COVID were assessed by STOP-PASC, a Phase 2 trial conducted at Stanford Medicine that was the first to determine if Paxlovid decreased symptoms of Long COVID. The primary objective of STOP-PASC was to assess the efficacy of a 15-day course of Paxlovid in reducing symptom severity of patients with PASC when compared to placebo treatments. The study also evaluated other signal-seeking secondary and exploratory objectives. Although participants safely tolerated Paxlovid administration, the drug did not demonstrate clinical benefit in PASC outcomes when compared to placebo-administered participants, and a substantial percentage of PASC patients were still experiencing symptoms after 15 weeks. Another study exploring high-dose coenzyme Q10 therapy demonstrated similar results to those of STOP-PASC. Participants in this randomized Phase 2 crossover trial demonstrated significant spontaneous improvement of symptoms regardless of treatment with Q10, but a substantial number of individuals still reported persistent symptoms at 20 weeks.

Results from STOP-PASC were likely complicated by drug-drug interactions with Paxlovid, vaccination events, COVID reinfections, and the sole inclusion of participants with documented COVID-19 cases. Despite these study design challenges, STOP-PASC demonstrated the feasibility of engaging and retaining patients through a complex and demanding study, provided an opportunity to generate a clinical dataset for multi-dimensional integration with exploratory data like biomarkers, and added to the understanding of Long COVID independent of clinical outcomes.

Moreover, the landscape of Long COVID trials remains dynamic and active across the globe. Several registered Long COVID clinical trials will assess potential therapeutic agents with various mechanisms of action (e.g., antivirals, monoclonal antibodies, other immunological interventions) and other trials will focus on nonpharmacological approaches, such as rehabilitation, psychotherapy, alternative medicine, and education. All future studies should prioritize patient and family perspectives, define more explicit clinical endpoints and biomarkers, and combine these efforts with other studies that evaluate the efficacy of repurposed medications or wearable devices in treating Long COVID.

Panel Discussion

Moderator: Dr. Eldrin Lewis, Stanford University
Panelists: Dr. Kanecia Zimmerman, Duke University; Dr. Upinder Singh, University of Iowa; Dr. Amy Proal, PolyBio Research Foundation

Long COVID Clinical Trial Landscape

The PolyBio Research Foundation is currently supporting multiple clinical trials, two of which are focused on pediatric populations. In one ongoing pediatric study at Harvard Medical School, SIMOA assays revealed the presence of SARS-CoV-2 spike protein in blood samples from children with MIS-C. Researchers postulated that viral reservoirs in the gut were the source of the spike protein levels, and they are now assessing the ability of larazotide—an approved medication that reinforces gut impermeability—to reduce blood spike protein levels in Long COVID pediatric patients. Enrollment in this study required participants to exhibit detectable spike protein in their blood samples, which provides a functional example of biomarker-based recruitment in a clinical trial.

Another ongoing pediatric clinical trial being conducted at the UCSF LIINC site is evaluating monoclonal antibodies that target pre-omicron strains of SARS-CoV-2. Although this trial is funded by the Patient-Led Research Collaborative, PolyBio is conducting gut biopsies to determine tissue levels of viral RNA before and after monoclonal antibody intervention. PolyBio is performing similar viral RNA assays as part of an ongoing Mount Sinai adult study, which assesses the FDA-approved HIV antiviral, Truvada®, as a treatment for symptoms related to both SARS-CoV-2 and Epstein-Barr virus. Truvada is also part of an ongoing Harvard multiple sclerosis clinical trial, which PolyBio has helped develop to encompass Long COVID.

Interpreting Clinical Trial Results

Studies like STOP-PASC should further assess individuals from previously studied patient populations who benefited from experimental treatment, despite those treatments failing to show a significant global benefit. Molecular analyses of samples collected from this participant subset may help identify Long COVID subtypes and related biomarkers as well as support future studies that enroll participants based on specific biomarker profiles. In addition, researchers should consider non-pharmacological mechanisms that may explain patient improvements. For example, many Long COVID patients had not received adequate care throughout their illnesses; thus, the high-quality care they received during STOP-PASC could have been what improved their health. Additionally, the disease burden of Long COVID and other IACCs can vary by

season, so patients involved in trials that began in the winter and ended in the spring may have experienced symptom improvement because of this seasonal transition.

Meaningful Patient Engagement in Clinical Trials

Patients helped develop RECOVER study designs by serving on protocol development teams and providing their perspectives to optimize study participants' experiences. Recruitment for RECOVER-NEURO and RECOVER-VITAL was so successful that they could not enroll all the volunteers who were interested in participating in the study. Harnessing this enthusiasm can help bolster enrollment for other RECOVER platforms as can recruiting via social media.

RECOVER-AUTONOMIC has had lower enrollment than the other two platforms, which may be due to required weekly participant visits as well as the late addition of an exercise protocol. Only one patient served on the AUTONOMIC study committee, and this individual did not see the study protocol before it was finalized, which indicates that patient participation on committees alone does not constitute meaningful patient engagement. To address this issue, study teams should use clear communication when designing future studies. Study teams can also expand meaningful patient engagement by involving bioethicists to ensure that patients fully understand all aspects of study participation. Trials should also recruit individuals with COVID-19 sub-phenotypes that current enrollment procedures may not capture.

Minimizing Burden of Clinical Trial Participants

RECOVER trials aim to minimize burden on study participants while maximizing patient safety, which may require in-person visits to optimize delivery of care. For example, IVIG treatments, which are part of RECOVER-AUTONOMIC, can have side effects that necessitate prompt, on-site medical attention. Similarly, professional medical settings are best for tissue biopsies and other sample collection, unless adequate resources exist that enable safe at-home collection. Decreasing visit durations can ease patient burden. RECOVER has decreased its visit durations by using virtual communication methods, such as email, to provide clinical health information. In addition, RECOVER platform designs have decreased in-person obligations by incorporating several remote participation opportunities. Although VITAL involves consistent, in-person visits, many of them are optional. Other RECOVER platforms only require two or three in-person visits, and NEURO was designed to be fully remote.

Researchers should always consider participant burden, regardless of whether a study is fully remote. Study teams should offer patients care throughout their study participation, especially because their participation can prevent patients from exploring other potentially more beneficial treatment options. Additionally, Long COVID patients may not be able to complete study assessments that are too time-consuming or administered on cumbersome computer programs, even when an assessment is completed at home. Future trials should also compensate patients for their participation to decrease patient burden, which was effectively demonstrated in RECOVER-VITAL.

Selecting and Prioritizing Possible Interventions

Current Landscape
Dr. Julia Moore Vogel, Scripps Research Institute

Studying Long COVID comes with several inherent challenges. Long COVID is associated with over 200 recognized symptoms, which can be experienced in any number of combinations, and little is known about the mechanisms of action (MOAs) of Long COVID. While funding is available, years of research are required to gain a more complete understanding of the underlying causes of Long COVID. Research efforts are further complicated by the constellations of symptoms for Long COVID and multiple MOAs that require further investigation, both of which increase the number of potential therapeutics for consideration. However, clinical trials to test these potential therapeutics are limited by the number of available patients. Thus, coordinated research efforts, particularly clinical studies using combinatorial designs to test multiple therapeutic agents, can help expedite the development of treatments and improve patient outcomes.

To incorporate broad patient inclusion criteria (e.g., varying symptom clusters) while testing multiple therapeutics and combinations, a combinatorial elimination clinical trial design (i.e., a "playoff" style model) was proposed. Using this design, therapeutics would be compared against one another via the elimination of underperforming drugs and the progression of high performing therapeutics. For this trial design to function optimally, clinical trials need to use adequate placebos and be sufficiently powered to effectively analyze data through noise.

Leveraging patient feedback to identify meaningful research opportunities was suggested. A list of crowdsourced symptoms developed from patient feedback, MOAs, and therapeutics of interest to patients was presented, including symptomatic viral persistence, mitochondrial dysfunction, microbiome dysbiosis and translocation, thromboinflammation, neuronal inflammation, microglial activation, hypothalamus-pituitary-adrenal axis-related MOAs, and relevant IACCs (e.g., POTS, ME/CFS). The list also includes proposed therapeutic agents relevant to these targets, such as using remdesivir for viral persistence or beta blockers to treat POTS. Intervention priorities based on patient feedback were shared, which indicate that patients prefer research efforts geared toward developing a cure rather than limiting research to managing symptoms. People with lived Long COVID experience want to make informed decisions regarding their care and whether to participate in clinical trials. They weigh the risk of exacerbating their symptoms or risking exposure and re-infection with SARS-CoV-2 if they participate in certain trials. The importance of conducting clinical trials of both repurposed and novel therapeutics was stressed. Importantly, clinical trials need to be developed with the goal of improving the quality of life for those with Long COVID and researchers should not allow perfection to be the enemy of progress.

Food and Drug Administration and National Center for Advancing Translational Sciences CURE ID for Long COVID
Heather Stone, FDA

As it requires an average of 10 to 12 years of research and over $1.2 billion to develop novel drugs, the absence of approved therapies often leads the medical community to explore repurposing existing drugs. However, data from repurposed drugs are rarely captured in a systematic way or in a way that enables the aggregation of patient data. In 2013, to accelerate the identification and development of potentially effective treatments for diseases lacking adequate approved therapies, FDA and the NIH National Centers for Advancing Translational Sciences (NCATS) developed CURE ID. CURE ID is a web-based treatment registry that allows patients, caregivers, and health care providers to report on repurposed drugs' treatment experiences and associated outcomes. In January 2024, CURE ID expanded to enable patients and caregivers to report treatment experiences related to Long COVID.

To gather real-world data, patients, caregivers, and clinicians register with CURE ID and submit reports of symptoms, treatments sought, and their outcomes using a combination of guided surveys, which are then reviewed, aggregated, and made available to anyone using CURE ID. Notably, CURE ID also includes data automatically extracted from EHRs for more than 130,000 acute COVID-19 cases. Together with patient-reported data, this information can be used to identify new combinations of drugs, dosing regimens, and durations, as well as new populations who may benefit from certain treatments. Researchers can use these data to identify symptoms or treatments of interest for further research, and patients can provide information on treatments that did not alleviate symptoms or had harmful results.

Currently, CURE ID faces several challenges that limit its usability, including its small user population and its reliance on patient-, caregiver-, and clinician-submitted data that lack true experimental control. These challenges result in both increased noise and reduced representation of the symptoms and treatment opportunities available. CURE ID represents a powerful tool for patient engagement and data aggregation, and further engagement with CURE ID will lead to more representative samples of Long COVID symptoms and treatments being explored by patients. In addition to providing a repository for patient- and clinician-reported treatment experiences, CURE ID may aid in the identification of drug combinations that have synergistic effects, as well as in the selection and prioritization of candidate treatments for further research in well-controlled clinical trials. Moreover, CURE ID could be used to identify areas of interest to patients.

Lessons from ACTIV Agent Prioritization
Dr. Timothy G. Buchman, Emory University

The ACTIV public-private partnership was formed in 2020 to identify, prioritize, and test treatments and vaccinations for COVID-19. A collaboration of more than 30 Federal government, industry, and nonprofit organizations, ACTIV was organized into four WGs, including the Clinical Therapeutics WG, which was further divided into the Agent Prioritization and Master Protocol subgroups.

The Clinical Therapeutics WG reviewed publicly available data on drugs that investigators identified for further research and incorporated feedback from SMEs to prioritize these therapeutics for evaluation in ACTIV-supported clinical trials. ACTIV reviewed more than 800 therapeutic agents—including antivirals, immunomodulators, supportive therapies, and neutralizing antibodies—and prioritized 37 of these agents for clinical trials under ACTIV master protocols. Of those 37 identified therapeutics, 17 had entered ACTIV-supported clinical trials by May 2021, just 12 months after the onset of the pandemic, and 6 of these prioritized therapeutics have shown efficacy as treatments for COVID-19 including infliximab, abatacept, Brii-196/Brii-198, LY-CoV-555, unfractionated and low-molecular-weight heparin, and intravenous administered AZD7442. Each of these agents manage the general immune response or assist with anticoagulation.

Several lessons have been learned from ACTIV trials, including positive lessons about involving participants who are committed to collaboration and communicating with global entities to improve data sharing and cross-organizational efforts. However, additional collaborations could further streamline research efforts and enrollment in clinical trials as the lack of a pre-established platform delayed the ability of ACTIV to identify therapeutic candidates. Early efforts that focused on complex mechanisms could have been supported by other foundational research exploring accessible mechanisms or treatment opportunities.

RECOVER-TLC Agent Submission Portal
Dr. Stacey Adam, FNIH

The RECOVER-TLC Intervention Information Submission Portal, which has been designed to build on processes developed and lessons learned during ACTIV, will identify and target therapeutics that can be used to treat Long COVID. The portal will collect a submitter's identifying information, affiliation, and contact information and the name of the intervention that they would like to nominate for further study. An adaptable survey, based on basic information provided by the submitter, will then guide respondents to provide additional data, such as impacted symptoms and reasons why the therapeutic should be studied further. The portal is intended to be freely available to researchers, clinicians, patients, and other members of the public.

A draft of prioritization criteria was shared that will be used to determine whether a therapeutic should be studied further. The draft criteria include the candidate therapeutic's rationale, stage of development, targeted symptoms or syndromes, pediatric approval status, data on use by pregnant and/or lactating people, clinical efficacy, safety, and scalability. The portal was launched on September 29, 2024. A RECOVER-TLC webpage is currently housed on the FNIH website that contains details on the initiative. Additionally, a public Request for Information (RFI)was issued in the NIH Guide for Grants and Contracts on October 28, 2024.

Panel Discussion
Moderator: Dr. Sarah Read, NIAID
Panelists: Dr. Julia Moore Vogel, Scripps Research Institute; Heather Stone, FDA; Dr. Timothy G. Buchman, Emory University; Dr. Stacey Adam, FNIH; Dr. Josh Fessel, NCATS; Meighan Stone, Long COVID Campaign

Clinical Trial Design
Panelists and Workshop participants noted that even small amounts of funding used appropriately can result in impactful research opportunities. Foundational biology studies can inform impactful clinical research by identifying MOAs, potential biomarkers, and underlying pathobiology. Additionally, clinical trials can be made more impactful by prioritizing studies of candidate therapeutics that are available, accessible, and likely to gain approval from government regulatory organizations for widespread use. Importantly, researchers must ensure that individuals randomized to control arms receive the same treatment opportunities as those randomized to intervention arms. Control patients could be enrolled in waiting lists and given access to the highest-performing therapeutics following the conclusion of a clinical trial, to ensure that all participants are given an opportunity to access treatments.

Portal Design
Workshop participants offered the following recommendations for improving data collection via CURE ID and the RECOVER-TLC Intervention Information Submission Portal:

- Capture age-related data for easier identification of therapeutics that support pediatric populations;
- Capture information related to pregnant populations or those seeking to become pregnant; and
- Follow up with people who previously submitted information via these portals to determine whether their outcomes are lasting or could have resulted from cyclical symptom severity.

RECOVER-TLC Trial Design Challenges

Populations
Dr. Sally Hodder, West Virginia University

Recently, surveillance systems and epidemiological evaluations have identified the populations who have a higher likelihood of developing Long COVID. Those populations are females or people who: (a) were hospitalized for acute COVID-19; (b) had underlying health conditions prior to contracting acute COVID-19; (c) have a lower SES, or (d) did not receive a COVID-19 vaccine. Additionally, older age correlates with a higher likelihood of Long COVID-related ailments with: (a) adolescents showing a higher likelihood compared to younger children; (b) middle-aged adults showing a higher likelihood of exhibiting Long COVID symptoms compared to younger and older adults; and (c) older adults showing a higher likelihood of developing incident conditions compared to younger adults. In addition, U.K. population data found that

individuals: (a) 45 to 54 years old; (b) with the lowest deprivation index scores; or (c) not seeking work had the highest incidence of self-reported Long COVID.

Recent surveillance data also show variations in the regional prevalence of Long COVID. In the U.S., West Virginia had the highest prevalence of self-reported Long COVID among adults over 18 years old, and the U.S. Virgin Islands had the highest prevalence among the U.S. territories. In addition, the number of NIH-funded COVID prevention and treatment clinical trials in fiscal year 2021 was inversely correlated with Long COVID prevalence across states. Moreover, a 2022 survey found that U.S. rural areas had a higher prevalence of self-reported Long COVID (compared to large, central metropolitan areas), while an International Classification of Diseases (ICD) code analysis showed that rural areas had the lowest prevalence of Long COVID diagnoses, indicating a high prevalence of undiagnosed Long COVID in rural areas.

When designing clinical trials for Long COVID, researchers should consider methods to ensure the inclusion of underdiagnosed and underrepresented populations as well as children and adolescents. In addition, researchers should consider recording defined phenotypes, the duration of Long COVID, the viral variant at the time of infection, and disease severity for each trial participant. Lastly, clinical trials should ensure that individuals with low SES have access to efficacious Long COVID treatment agents posttrial.

Panel Discussion on Populations
Moderator: Dr. Sally Hodder, West Virginia University
Panelists: Angela Meriquez Vazquez, Children's Partnership; Dr. Sharon Saydah, CDC; Dr. Helen Ward, Imperial College

Underrepresented Populations
Clinical trials often lack representation from the populations who are most impacted by disease, such as individuals who are homebound due to disease severity and unable to travel to study sites. Researchers should consider designing clinical trials that allow homebound individuals to participate by sending community workers or research staff to homes for biomarker measurement and collection. Furthermore, clinical trials can include digital measures for at-home data collection, such as smartphone applications, although researchers should provide unique support for certain populations. For example, in populations with low SES, researchers should consider that patients may struggle to obtain internet access for digital measures. Researchers should also consider increasing study participation in rural areas by decentralizing clinical trials to include rural hospital study sites.

Addressing Stigma and Toxic Stress
Clinicians often hesitate to diagnose patients with Long COVID due to the belief that a diagnosis is not beneficial when treatment options are limited or do not exist. Furthermore, Long COVID patients often feel dismissed or unheard when communicating with clinicians about their symptoms (e.g., clinicians downplaying symptoms) and parents and caregivers often resist accepting Long COVID diagnoses of those they provide care for due to stigma surrounding the disease. Long COVID stigma also contributes to toxic stress, which is especially harmful to

children and adolescents due to its potential impacts during critical periods of brain development.

The Long COVID health care community should develop diagnostic protocols and guidelines for educating clinicians and caregivers about the benefits of a Long COVID diagnosis, e.g., referrals to specialists, and symptom-based treatment options that are currently available. In addition, researchers and clinicians should create supportive and empathetic environments during clinical exams and clinical trials. Community health workers also can help to address Long COVID stigma by supporting patients through the diagnostic and treatment processes, which can then build community trust and subsequently help recruitment for clinical trials. As it is critical to build trust, researchers must involve patients early and in every step of the research process (e.g., identifying underrepresented populations and relevant clinical endpoints), rather than simply surveying patients to finalize clinical trial design.

Study Designs
Dr. Priscilla Hsue, University of California Los Angeles

To exemplify a type of clinical trial design in an ongoing Long COVID study, a description of the randomized, double-blind, placebo-controlled trial, EValuating Baricitinib on PERsistent nEurological and Cardiopulmonary Symptoms of Long COVID (REVERSE-LC) was provided. This is a Phase 3 clinical trial that is evaluating the Janus kinase (JAK) 1/2 inhibitor, baricitinib, for treating Long COVID. Baricitinib is FDA-approved for treating rheumatoid arthritis and alopecia areata, has a known safety profile, and is currently being evaluated in persons living with HIV for its impact on neurocognitive function and viral reservoirs. In prior clinical trials of acute COVID-19 treatment, baricitinib in combination with remdesivir showed higher efficacy than remdesivir alone, particularly among participants receiving high-flow oxygen therapy or noninvasive mechanical ventilation. Furthermore, baricitinib benefited patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO), with a safety profile similar to standard of care, and reduced mortality among hospitalized COVID-19 patients.

The first REVERSE-LC study cohort includes 500 participants with a confirmed SARS-CoV-2 infection at least six months prior to trial enrollment, while the second cohort includes 50 participants with suspected SARS-CoV-2 infection, but no positive COVID-19 test. Participants from both cohorts exhibit self-reported cognitive impairment using the Everyday Cognition Scale. Participants were excluded from the study if they had active cancer in the last five years, had a venous thromboembolism in the past six months, were pregnant or intended to become pregnant during the study, or had a chronic tuberculosis, hepatitis, or uncontrolled HIV infection.

REVERSE-LC's primary objective is to determine whether baricitinib improves cognitive outcomes using the Central Nervous System Vital Signs test, a cognitive battery composed of validated and robust neuropsychological tests. Secondary endpoints include cardiorespiratory fitness during maximal exercise, the 6-Minute Walking Test to assess aerobic capacity and endurance during submaximal exercise, and questionnaires to evaluate subjective measures (e.g., quality of life, PEM, subject cognitive and mental health). Exploratory endpoints include

evaluation of inflammatory markers in various biospecimens (e.g., plasma, PBMCs, and CSF), neuroimaging of brain structure, and autonomic dysfunction assessments.

Panel Discussion on Study Designs
Moderator: Dr. Dean Follmann, NIAID
Panelists: Dr. Priscilla Hsue, University of California Los Angeles; Dr. Christopher McAleer, AIM Immunotech; Dr. Tom Patterson, University of Texas San Antonio; JD Davids, Strategies for High Impact; Lauren Stiles, Dysautonomia International

Studying and Treating Multiple Aspects of Long COVID
As Long COVID is a multifaceted disease, a single therapeutic is unlikely to address all symptoms of the disease or benefit all Long COVID populations. Clinical trial designs should incorporate deep phenotyping to understand specific aspects of Long COVID and to identify subpopulations that may require specific therapies. Furthermore, researchers should consider observational studies to help identify subpopulations. Although preexisting comorbidities may confound clinical trial results, researchers should also ensure that FDA-approved therapeutics do not exclude individuals with comorbidities because individuals with preexisting conditions are more likely to develop Long COVID after acute SARS-CoV-2 infection.

To further address all aspects of Long COVID, researchers should consider platform trials to facilitate the evaluation of multiple therapeutics and combinatorial approaches. For example, the Adaptive COVID-19 Treatment Trial (ACTT) used a platform trial design to assess the effectiveness of multiple therapeutics for acute COVID-19 treatment. The ACTT team developed a master protocol and contract for all study sites, which allowed the team to rapidly transition from testing one therapeutic to another without significant study modifications. In addition, the platform design enabled international collaborations and the rapid incorporation of curated community feedback into study protocols. Leveraging this platform approach for testing potential Long COVID treatments may help to accelerate FDA approval for multiple therapeutic approaches.

Inclusion of Transgender and Non-Binary Populations
Researchers should consider including transgender and non-binary individuals, who are disproportionally impacted by Long COVID, in clinical trials. Moreover, leaders and patient advocates from transgender and non-binary communities should be consulted throughout the research process and hold clinical trial board memberships to provide input on study design. Research and clinical staff should ensure representation from transgender and non-binary individuals to support participants and provide a comfortable and welcoming study environment. In addition, researchers should consider conducting nested sub-studies in which transgender and non-binary community health workers can evaluate participant retention and quality of life during and after clinical trials. Meeting participants highlighted several advocacy groups that researchers can contact for clinical trial input, including Long COVID Justice (connect@s4hi.org), the Office of HIV/AIDS Network Coordination (HANC), the NIAID Division of AIDS (DAIDS), and the Transgender Professional Association for Transgender Health (TPATH).

Endpoints
Dr. Alison K. Cohen, UCSF

Researchers must consider the diversity of clinical outcomes that are important to patients, as well as how to operationalize those outcomes into standardized validated measures. Endpoints of potential interest include measures of functional capacity, PEM, cognitive impairment, and viral persistence. However, Long COVID clinical trials often do not share the same endpoints, creating barriers to analyzing across datasets from multiple trials. Thus, researchers should coordinate endpoint selection and develop CDEs to facilitate data analysis.

Researchers also should consider developing Long COVID endpoints relevant to specific populations and discern how particular endpoints may limit clinical trial participation. For example, individuals exhibiting severe symptoms may opt out of trials with long in-person data collection visits. Furthermore, because in-person data collection may trigger PEM, researchers should carefully select which data require in-person collection. In addition, researchers should engage patients in endpoint selection and consider time horizons for endpoint measures. Overall, ideal clinical trial endpoints should be measurable, meaningful to patients, and support regulatory decision-making.

Panel Discussion on Endpoints
Moderator: Dr. Adrian Hernandez, Duke University
Panelists: Dr. Alison K. Cohen, UCSF; Dr. Seth Lederman, Tonix Pharmaceuticals; Dr. Linda Geng, Stanford University; Dr. Todd Davenport, University of the Pacific; Dr. Paul Lee, FDA

Identifying Subclassifications of Long COVID
Over time, the oncology research community has identified many cancer indications and developed therapeutics to specifically target MOAs for each indication. Similar to cancer, Long COVID symptomology is complex and heterogeneous among patients, highlighting the need to identify subclassifications. Oncology research processes can serve as an example to Long COVID researchers on developing multiple therapeutics for Long COVID subclassifications. The Long COVID research community can accelerate identification of these subclassifications by selecting core CDEs that each clinical trial can collect to aid in cross-study analyses. Researchers can also model Long COVID CDEs from CDEs used in the NIH Helping to End Addiction Long-term (HEAL) Initiative.

Accelerating FDA Approvals
In addition to identifying cancer indications, the oncology research community has collaborated with the National Cancer Institute (NCI) and FDA to develop regulatory policies that both accelerate approvals of new cancer therapies and allow pharmaceutical companies to market therapies before receiving full FDA approval. Researchers should consider collaborating with FDA to develop similar policies that could accelerate approvals of novel Long COVID therapeutics, which would enable researchers to leverage short-term opportunities to address specific Long COVID symptoms while obtaining long-term data on the therapeutics' underlying biological mechanisms.

Selecting Common Primary Endpoints

In oncology research, progression-free survival is one of the most used primary endpoints in clinical trials evaluating novel cancer therapies, which has helped accelerate FDA therapy approvals. Research should similarly identify a common primary endpoint for Long COVID clinical trials. Importantly, researchers can further accelerate these trials and FDA approvals by implementing relevant preexisting and validated endpoints, such as self-reported Patient Global Impression of Change and the Chalder Fatigue Scale. However, researchers must also consider how patient fatigue and PEM that are triggered by in-person trial participation could confound results from endpoints based on measures of fatigue. In addition, researchers should select common longitudinal endpoints that capture the progression of symptomology over time. FDA provides patient-focused drug development guidance that may benefit researchers in selecting relevant endpoints for regulatory approvals.

Pediatric Trials

Dr. Melissa Stockwell, Columbia University

Long COVID is a significant pediatric public health problem. Several studies have shown an estimated 2 to 10 percent prevalence of persistent COVID-19 symptoms among pediatric patients after SARS-CoV-2 infection, and the negative impacts of Long COVID on children and families within health care, education, social settings, and finances. However, most current knowledge on Long COVID has been gathered from studies of adults. There are 11 ongoing clinical trials across the world enrolling pediatric patients, with five of those trials also enrolling adults.

RECOVER-Pediatrics is a retrospective and prospective longitudinal, observational study that aims to improve the understanding of Long COVID in pediatric patients. Currently, the study has enrolled 22,577 pediatric patients from diverse backgrounds across four distinct cohorts: (a) *de novo RECOVER prospective cohort* of children and young adults ages birth through 25 years with or without a known history of SARS-CoV-2 infection (the main cohort); (b) *Adolescent Brain Cognitive Development (ABCD) extant cohort* of patients 12 to 17 years old with or without post-acute infection; (c) *in utero exposure cohort* of children less than 3 years old with or without maternal infection; and (d) *COVID Multisystem Inflammatory Syndrome In Children (MUSIC) Study extant cohort* of newborn patients with MIS-C.

RECOVER-Pediatrics has enrolled over 2,000 participants who likely have Long COVID and are deeply phenotyped with known baseline characteristics. In the first publication of RECOVER-Pediatrics data, researchers compared symptoms between individuals with and without a history of SARS-CoV-2 infection and revealed that pediatric symptoms affected nearly all organ systems and were distinct from adult symptoms. The study also identified several phenotypic clusters among school-age children (6 to 11 years old) and adolescents (12 to 17 years old):

- School-age children showed (a) trouble with sleeping, memory, and focusing, and (b) abdominal pain and nausea or vomiting
- Adolescents showed changes in or loss of smell or taste

- Both school-age children and adolescents showed overlapping phenotypes of (a) symptoms across multiple organ systems and (b) pain, fatigue, and low energy

These overall findings suggest that children and adolescents have Long COVID symptoms and phenotypic clusters that are distinct from adults. This highlights the need for pediatric-specific interventions and clinical trial outcomes, as well as continued data analysis and pathobiology studies to support mechanistic insights into pediatric Long COVID. In addition, researchers should establish a process for prioritizing clinical trials of potential pediatric-specific interventions to address symptom relief, including testing existing pharmacological and non-pharmacological interventions. Researchers should also create a flexible clinical infrastructure to accommodate new findings and studies and consider designing platform trials.

Panel Discussion on Pediatric Trials
Moderator: Dr. Sindhu Mohandas, Children's Hospital Los Angeles
Panelists: Dr. Melissa Stockwell, Columbia University; Dr. Roberta DeBiasi, Children's National; Dr. Gail Pearson, NHLBI

Pediatric Trial Design
Due to potential developmental effects in children, Long COVID may have a greater impact on children than adults, which underscores the urgency to begin pediatric trials. Some Long COVID trials are testing FDA-approved drugs (e.g., anti-inflammatory medications, immunomodulators) with known safety profiles in children, which can accelerate pediatric trials by eliminating the need for additional safety studies. However, despite potential similarities in underlying biological mechanisms of Long COVID between children and adults, researchers should consider how different clinical trial outcomes for pediatric participants could affect trial design. Researchers should also aim to stratify pediatric populations by age, when feasible, as well as by phenotypic clusters within each age group, and they should develop platform trials to facilitate the testing of multiple therapies that address various pediatric targets and phenotypic clusters. Additionally, the Long COVID research community should ensure a sufficient number of non-placebo-controlled trials are conducted, particularly because the time required for randomization in placebo-controlled trials can confound the interpretation of study results due to developmental changes that may occur in children during randomization.

Trial Recruitment and Participant Motivations
Although pediatric trials present unique challenges compared to adult trials, pediatric trials also present unique opportunities and advantages. Pediatric researchers often find that both pediatric patients and their parents are highly motivated to participate in trials, especially because parents express high concern about resolving their child's condition. Researchers should consider implementing flexibility in trials, such as flexible times for study visits, accommodations for children's schoolwork, and the remote collection of measures. One example of remote collection is the use of iPads for surveys and outcome measures, which children may enjoy. In addition, researchers should properly educate pediatric participants about the research surrounding clinical trials to provide them with a unique educational experience and a sense of community engagement.

Panel Discussion on Overall Trial Design Challenges
Moderator: Dr. Sally Hodder, West Virginia University
Panelists: Dr. Kanecia Zimmermann, Duke University; Dr. Jerry Krishnan, University of Illinois at Chicago; Dr. Catherine Blish, Stanford University

Antiviral Therapies
Whether or not mechanistic research reveals that viral persistence is a direct driver of Long COVID, researchers should exercise caution when interpreting results from clinical trials testing antiviral therapies. For example, several antiviral medications stop viral replication late in the replication cycle, resulting in continued replication of viral RNA and subsequent protein production that can drive inflammation despite the absence of virion. Thus, if antiviral therapies fail to suppress viral detection, or succeed but symptoms persist, researchers should consider using immunomodulators in combination with antiviral therapies instead of abandoning antivirals. In addition, researchers should consider testing antiviral therapies that target early viral replication to avoid continued replication of viral RNA.

Enhancing Trial Recruitment
To enhance clinical trial recruitment, researchers should focus on the patient perspective, the experience of trial participation, and methods of patient reciprocity. First, researchers should treat patients and their health care providers as partners in clinical trials by involving them in various trial workstreams, such as problem-solving recruitment challenges in early study design. Furthermore, researchers should survey patients on their experiences from other clinical trials and implement positive experiences in trial design.

Next, researchers should build reciprocal relationships with patients by aligning interests, providing patients with financial compensation (including travel costs), and providing individual-level trial data to patients. However, providing patients with trial data may affect the blindness of analyses and study integrity. Furthermore, sharing data from observational studies may have different impacts on study integrity compared to clinical trials. When making decisions about what data to share, researchers should include patients in the decision-making process and educate the community about why certain data have remained confidential. In addition, researchers should ensure that trial data are communicated using understandable language and media that builds trust. For example, patient portals often do not provide sufficient descriptions of laboratory results and may make patients feel disconnected from the research team.

Researchers also should educate local communities about clinical trial processes. Similar to communicating trial results to patients, communication for local communities should use language that is understandable and does not stigmatize patients. For example, recruitment messages describing the harms of Long COVID may not be as effective as messages describing the benefits of Long COVID treatment. In addition, within pediatric populations, many families may not understand that children can be diagnosed with Long COVID. Thus, messages that frame clinical trials as recruiting for “children with persistent fatigue or lack of focus during school after a [SARS-CoV-2] infection” may increase pediatric study participation. Together,

these recruitment strategies can help build trust between researchers, patients, and local communities, and subsequently combat misinformation about research.

Regulatory Perspectives

Food and Drug Administration
Dr. John Farley, FDA

Along with ensuring that the benefits of new therapeutics outweigh their risks for intended use, FDA also aims to facilitate drug development as efficiently as possible in order to increase drug availability to patients. FDA has two primary regulatory checkpoints in the drug development process: (a) investigational new drug (IND) application submissions to begin clinical trials after the completion of preclinical testing, and (b) new drug application (NDA)/biologics license application (BLA) submissions after the completion of Phase 3 trials. FDA has many experts on disease and current FDA-approved drugs who are available to meet with Sponsors and investigators early and often before IND and NDA/BLA submissions. FDA can also provide advice to sponsors and investigators prior to initiating and during the conduct of clinical trials.

To support regulatory approvals, FDA requires substantial evidence that a drug shows the effect that the sponsor purports, which FDA interprets as generally requiring at least two clinical trials. Additionally, FDA defines several characteristics of an adequate and well-controlled clinical trial in accordance with 21 CFR 314.126. For Long COVID trials, sponsors should focus on enhancing diversity in patient racial and ethnic backgrounds. However, through inclusion and exclusion criteria, sponsors should minimize pathophysiological heterogeneity that can mask efficacy signals. Data from only one trial may be adequate depending on its persuasiveness, understanding of disease pathophysiology, robustness of evidence, seriousness of the disease, size of the patient population, and the ethics and feasibility of conducting an additional trial.

To support drug efficacy, FDA requires that study endpoints be well-defined and reliable. Primary categories of endpoints include clinical endpoints (i.e., those demonstrating how a patient feels or functions) and surrogate endpoints (e.g., those demonstrating relevant biomarker changes). As the Long COVID research community has not yet identified a well-defined biomarker, clinical endpoints are currently the most advantageous for Long COVID clinical trials. However, biomarkers of Long COVID may be beneficial for proof-of-concept studies and, alongside clinical endpoints, can provide evidence to associate biomarkers with clinical benefit. In April 2023, FDA held a public meeting on patient-focused drug development for Long COVID that discussed patient-centered outcomes to help researchers select appropriate clinical endpoints for future clinical trials.

Several clinical outcome assessments (COAs) can be used as clinical endpoints in clinical trials. PROs are a COA based directly on patients self-reporting the statuses of their health conditions without someone else interpreting their responses. In the absence of well-defined biomarkers, PROs are likely to be the most beneficial endpoints in Long COVID clinical trials. FDA developed a 2009 PRO guidance document that outlines good measurement principles researchers should consider for well-defined and reliable PRO measures, and the FDA COA Roadmap outlines how

FDA determines that a COA is appropriate for clinical trial use. Additionally, researchers can apply lessons learned about developing PROs from acute COVID-19 studies to future Long COVID trials. FDA encourages sponsors and investigators to meet with FDA early and often during the COA development process.

European Medicines Agency
Dr. Marco Cavaleri, European Medicines Agency (EMA)

EMA collaborates with European Union patients, consumers, health care professionals, and organizations to ensure each party's perspective is reflected in all aspects of drug development. During the COVID-19 pandemic, EMA created the Emergency Task Force (ETF) to liaise with pharmaceutical companies and academic institutions to provide guidance on clinical development and study design. Currently, there are no EMA-approved medicines for the treatment or prevention of Long COVID, but EFT is helping companies develop treatment and prevention options. As part of its Big Data efforts, EMA is also exploring the feasibility of using real-world data to better understand Long COVID.

Significant regulatory challenges that EMA faces for Long COVID clinical trials include defining patient populations, treatment success, and appropriate primary efficacy endpoints. Developing an operational definition of a patient population for Long COVID is difficult due to the multisystemic nature of the condition and the unclear relevance of pathophysiological mechanisms. EMA recommends that researchers consider the (a) inclusion of patients with symptoms of Long COVID acquired from other disease origins (e.g., POTS, ME/CFS); (b) inclusion of patients with identified risk factors for developing Long COVID; (c) role of biomarkers in defining inclusion criteria; and (d) different eligibility criteria for various phenotypic clusters, patient age groups, and times of disease onset.

For outcome measures, Long COVID researchers face challenges with endpoint definitions that reflect clinically meaningful response and longitudinal change, endpoints that differ for treatment trials compared to prevention trials, symptom-specific endpoints, and endpoints for interventions with differing MOA. EMA currently considers PROs as the best option for primary endpoints in Long COVID clinical trials, and it prefers that researchers use well-known PROs that are validated for Long COVID, with any novel PROs being similarly validated for detection of clinically meaningful changes in patients. Although clinical evidence supporting the use of biomarkers as surrogate endpoints is lacking, biomarkers are important for proof-of-concept studies to confirm MOA and the biological plausibility of potential treatments. Moreover, biomarkers are useful for enriching study populations who will benefit from specific treatments. Further information about EMA suggestions for Long COVID treatment and prevention trials can be found in a recently published workshop outcomes article.

Panel Discussion
Moderator: Dr. Jeanne Marrazzo, NIAID
Panelists: Dr. John Farley, FDA; Dr. Marco Cavaleri, EMA

Accelerated Approval Pathways
During the COVID-19 pandemic, FDA leveraged Emergency Use Authorization (EUA) to facilitate the availability, use, and subsequent regulatory approval of COVID-19 vaccines and treatments for acute SARS-CoV-2 infection (e.g., the market release of Paxlovid before its FDA approval). However, FDA is not authorized to initiate EUAs, and all drugs made available to patients under EUA still require substantial safety and efficacy evidence after their accelerated market release phase. Given the urgent need for Long COVID treatments and prevention therapies, FDA and EMA may consider allowing accelerated approval processes, such as those implemented for serious, life-threatening diseases.

To further facilitate drug approvals, sponsors can submit IND questions to FDA and EMA simultaneously. FDA and EMA will then collaborate to address a sponsor's IND questions and any conflicting IND requirements that may arise between the two agencies. This form of collaboration commonly occurred during the pandemic, and both agencies seek to continue such collaboration for Long COVID research. In addition, NIH's continued engagement in Long COVID research can help de-risk drug development by providing biological mechanistic insights from preclinical studies. Long COVID research can also gain insights from case studies of clinicians prescribing FDA-approved drugs for unapproved (i.e., off-label) use in the treatment of Long COVID patients, which can provide additional evidence of safety and efficacy for subsequent FDA approval of repurposed drugs. For example, a large body of literature is available supporting the off-label use of corticosteroids during the pandemic, which has significantly enhanced clinical protocols for acute COVID-19 treatment.

Long COVID as Drug Indication
NASEM recently published a definition for long COVID as a disease. While this definition may help FDA and EMA approve drugs for a specific "Long COVID" indication, the complexity and heterogeneity of the disease presents a distinct challenge in creating a well-defined regulatory indication. Observational and clinical studies that identify subpopulations of Long COVID patients can help to further refine NASEM's definition and accelerate the process of creating Long COVID-specific drug indications.

Regulatory Guidance for Defining Endpoints
Recently, FDA sought input from patients on defining clinically meaningful changes as measured by clinical endpoints. FDA acknowledges that patients' perspectives are critical for understanding drug efficacy, and, as such, FDA includes patients in their advisory committees to drive discussions about identifying the most important clinical benefits from Long COVID treatments. Researchers should consider implementing secondary endpoints (e.g., molecular and neuroimaging biomarkers) to aid preclinical studies in elucidating Long COVID mechanisms. Although acute COVID-19 clinical trials used unique primary endpoints, such as viral clearance, Long COVID trials can implement other acute COVID-19 endpoints as secondary or exploratory

endpoints. However, researchers should define secondary endpoints for Long COVID subpopulations before initiating trials to avoid having to repeat trials to obtain data on specific subpopulations. As a next step, FDA will convene public workshops to collaborate with industry and academia about how recent findings on Long COVID mechanisms may inform endpoint selection. EMA will continue hosting similar workshops to motivate the initiation of international clinical and platform trials, as there are no ongoing Long COVID trials in European countries.

How Do We Get from Here to the Next Patient-Centered Long COVID Clinical Trials
Lisa McCorkell, Patient Led Research

Multiple key areas for RECOVER-TLC to help develop future patient-centered Long COVID clinical trials were highlighted, including patient engagement, intervention selection, trial design, and endpoint selection. RECOVER-TLC should incorporate meaningful patient engagement throughout trial conduct, including in a trial's design and review processes. Researchers should also consider patient input when determining clinical trial eligibility criteria, as well as assessment scoring to harmonize interpretations of "safety" and "clinical efficacy" between patients and researchers. Furthermore, Long COVID clinical trials should have diverse patient and caregiver representation on advisory committees, and researchers should curate patient input when selecting patient committee members.

Long COVID clinical research will require both platform trials and smaller experimental and proof-of-concept trials. RECOVER-TLC should establish funding mechanisms for both trial types, especially for trials conducted outside of the RECOVER-TLC network. Clinical trials also provide opportunities to collect data on exploratory endpoints to probe biological mechanisms underlying Long COVID. Importantly, curative interventions are the top priority for patients and must be accessible to a wide range of patient populations. When designing trials, researchers should consider medication interactions, the need for prior treatment to stabilize symptoms, patient comorbidities, trial impacts on symptoms and disease severity (e.g., illness duration, seasons, mast cell and PEM triggers), and the inclusion of non-COVID IACCs as comparator groups. To enable appropriate endpoint selection, researchers need to validate PROs, continue to study and develop objective biomarkers, implement disability justice principles and trauma-informed practices, and return individual results to patients. Researchers also have a responsibility to the patient community to meet patients where they live, as well as consider trial safety (e.g., masking), digital equity, compensation, gender-affirming and culturally competent care, and patient trust.

For more details about designing patient-centered Long COVID trials, researchers can refer to a recently published paper authored by multiple patients and patient advocates.

Panel Discussion
Moderators: Dr. John Beigel, NIAID
Panelists: Lisa McCorkell, Patient Led Research; Dr. Laurie Gutmann, Indiana University School of Medicine; Dr. Clint Wright, NINDS; Dr. Yves Rosenberg, NHLBI; Dr. Eldrin Lewis, Stanford University

Panelists and meeting participants highlighted strategies for enhancing patient-focused Long COVID clinical trials, emphasizing the need to: expand clinical trial inclusion criteria; study Long COVID across the entire lifespan; design appropriate clinical trials and outcome measures; build trust between researchers and patients; develop a broad Long COVID clinical trials network; and increase funding opportunities.

Several patients, caregivers, and patient advocates also emphasized the urgent need to begin clinical trials now and to ensure that all participants are provided adequate compensation for time and travel investments, have opportunities to participate in clinical trials from home, and have equitable access to individual-level data.

RECOVER-TLC Next Steps and How to Proceed

Key Considerations
Following the discussion, Dr. Marrazzo summarized the following key considerations and concerns raised during the meeting:

Communication and Patient Engagement

- Patient and community involvement is critical to all aspects of planning clinical trials, ranging from intervention selection, trial design and conduct, results interpretation and dissemination, and implementation of findings.
- There is significant value in assembling meetings with diverse individuals who are passionate about improving the lives of those living with IACCs. Furthermore, discussions during these meetings can be both robust and respectful.
- Clinical trials leadership must be accountable and transparent through the entire clinical trials process. An opaque, top-down approach to the clinical trial process undermines trust and willingness of patients to collaborate with researchers.
- Researchers should act urgently to begin clinical trials without sacrificing scientific rigor, but they should also recognize the amount of effort and energy required for patients to participate in clinical trials, especially for those with limited resources.
- RECOVER has significantly advanced the research community's understanding of Long COVID, and clinical trials should leverage RECOVER findings for future success.
- Health care providers are under resourced to provide evidence-based, comprehensive care to Long COVID patients.

Selection of Clinical Trials

Researchers designing Long COVID clinical trials should consider:

- Minimizing exclusion criteria
- Ensuring participation and access for children, adolescents, and reproductive-aged women
- Including patients diagnosed with other IACCs
- Recognizing that multimodal interventions may be required, given the broad spectrum of Long COVID pathobiology and symptomology
- Building on and expanding the RECOVER infrastructure
- Expanding participation access to all patients, including access beyond standard work hours (e.g., 9:00 am to 5:00 pm), despite the severity of patient symptoms
- Prioritizing interventions and determining whether certain clinical trials require a placebo arm

Linking Interventions to Pathobiology

- Despite RECOVER hosting a large biorepository, the Long COVID community still faces barriers to accessing data, interrogating a vast number of potential pathophysiology mechanisms, ensuring timely responses to proposals for sample use, and leveraging existing Long COVID research.
- Researchers should utilize other existing repositories.
- Researchers should consider the burden of biospecimen collection for patients participating in clinical trials.

Next Steps for NIH

Dr. Marrazzo reviewed NIH's plans to support RECOVER-TLC in the following areas:

Communication and Patient Engagement

- Provide discussion forums as regular opportunities to continue frequent Long COVID dialogues using a variety of formats (e.g., in-person and online), including monthly updates on Long COVID research in an accessible form for patients and an annual meeting to review research progress and strategy in a large discussion forum.
- Ensure meaningful participation of patients and advocates in clinical trial processes by using community engagement groups and working groups and consider regional strengths where existing investigators have already established patient relationships.
- Institute regular communication with the RECOVER team to build on existing clinical trial infrastructure.
- Finalize the RECOVER-TLC governance structure and organization by soliciting interest from and inviting committee members, selecting experts to review RECOVER-TLC materials and content, and centralizing leadership under NIAID's Office of the Director.
- Explore the possibility of developing and updating Long COVID treatment guidelines for health care providers.

Selection of Clinical Trials

- Assemble working groups with content expertise and lived experience.
- Develop a rigorous and rapid clinical trial review process.
- Assess the approaches implemented in ACTT and ACTIV frameworks to optimize RECOVER-TLC's approach to clinical trials, including their platform designs and other adaptive trial mechanisms.
- Collaborate with the RECOVER team and other COVID research networks to maximize existing Long COVID research infrastructure and work with FDA to define relevant endpoints that can support regulatory decisions.
- Ensure the inclusion of diverse populations, such as rural communities, by using emerging technologies to expand trial accessibility.
- Implement effective portfolio management to ensure the evaluation of the most promising and diverse interventions that have a strong rationale.

Linking Interventions to Pathobiology

- Urgently investigate how researchers can use existing biospecimens and data to address mechanistic questions that can inform clinical trial prioritization.
- Recognize diversity of expertise across disciplines and establish multidisciplinary basic science working groups, as needed.

Appendix A: Agenda

Monday, September 23, 2024

Retrospective lens of Long COVID, including lived experience, provider perspectives, state of the art updates, and summary of ongoing activities.

9:00 am **Welcome and Opening Remarks**
Dr. Monica Bertagnolli, NIH; Dr. Julie Gerberding, FNIH

9:15 am **Goals of the Workshop**
Dr. Jeanne Marrazzo, NIAID; Dr. Lindsey Baden, Brigham and Women's Hospital/Harvard University

9:30 am **RECOVER-TLC—Proposed Organizational Structure and Function**
Dr. Joseph Breen, NIAID

10:00 am **Living with Long COVID—Diverse Perspectives**
Christine Maughan, Patient Representative; Angela Meriquez Vazquez, Children's Partnership; Liza Fisher, Patient Advocate

10:45 am **Break**

11:00 am **Long COVID Definitions and Impact on Clinical Trials**
Dr. Jerry Krishnan, University of Illinois at Chicago

Panel Discussion
Moderator: Dr. Ian Simon, OASH

Panelists: Dr. Jerry Krishnan, University of Illinois at Chicago; Karyn Bishof, COVID-19 Longhauler Advocacy Project; Dr. Sharon Saydah, CDC; Dr. Serena Spudich, Yale University

12:00 pm **Lunch**

12:45 pm **Overview of Observational Studies—Implications for Clinical Trial Design**
Dr. Leora Horwitz, New York University

Clinical Data from the Observational studies
Dr. H. Clifford Lane, NIAID; Dr. Ziyad Al-Aly, Department of Veterans Affairs/Washington University in St. Louis

Panel Discussion

Moderator: Dr. Serena Spudich, Yale University

Panelists: Dr. Leora Horwitz, New York University; Dr. Mike Sneller, NIAID; Dr. Ziyad Al-Aly, VA/Washington University in St. Louis; Dr. Igor J. Koralnik, Northwestern University; Dr. Melissa Stockwell, Columbia University; Dr. Helen Ward, Imperial College; Dr. Simon Pollett, Uniformed Services University

2:00 pm **Break**

2:15 pm **Pathobiology Studies—What is Known, What Information is Needed, What are the Challenges to Providing the Basis for Future Clinical Trials**

Neural Inflammation/Immune Activation
Dr. Mike VanElzakker, Harvard University

Endothelial Injury, Thrombosis, Complement Activation
Dr. Resia Pretorius, Stellenbosch University

Viral Persistence
Dr. Michael Peluso, University of California San Fransisco

Biorepositories and Candidate Biomarkers by Pathway—Viral, Inflammatory, and Immunologic
Dr. Paul J. Utz, Stanford University

Panel Discussion
Moderator: Dr. Joseph Breen, NIAID

Panelists: Dr. Mike VanElzakker, Harvard University; Dr. Resia Pretorius, Stellenbosch University; Dr. Michael Peluso, University of California San Fransisco; Dr. Paul J. Utz, Stanford University; Dr. Amy Proal, PolyBio Research Foundation

3:30 pm **What Can Be Learned from Other Related Syndromes to Inform the Design of Long COVID Clinical Trials**

ME/CFS
Dr. Avi Nath, NINDS

POTS
Dr. Peter Rowe, Johns Hopkins University

MIS-C
Dr. Adrienne Randolph, Harvard University

4:00 pm **Panel Discussion on How to Use the Information from Observational and Pathobiology Studies, and ME/CFS, POTS, MIS-C, and Other Related Syndromes to Inform the Design of Future Clinical Trials**
Moderator: Dr. H. Clifford Lane, NIAID

Panelists: Hannah Davis, Patient-Led Research Collaborative; Jaime Seltzer, MEAction Network; Dr. Alba Azola, Johns Hopkins University; Dr. Ian Lipkin, Columbia University; Dr. Steve Deeks, University of California San Fransisco

5:00 pm **Adjourn for the Day**

Tuesday, September 24, 2024

Discuss path forward including prioritization of interventions, study design, end points, etc.

9:00 am **Recap of Monday Highlights**
Dr. Lindsey Baden, Brigham and Women's Hospital/Harvard University

9:15 am **Public Comment Period**

9:45 am **Leveraging Clinical Trials Already Underway or Planned**

Overview of RECOVER Clinical Trials
Dr. Kanecia Zimmerman, Duke University

Other Long COVID Trials—Landscape Overview
Dr. Upinder Singh, University of Iowa

Panel Discussion
Moderator: Dr. Eldrin Lewis, Stanford University

Panelists: Dr. Kanecia Zimmerman, Duke; Dr. Upinder Singh, University of Iowa; Dr. Amy Proal, PolyBio Research Foundation

11:00 am **Break**

11:15 am **Selecting & Prioritizing Possible Interventions**

Current Landscape
Dr. Julia Moore Vogel, Scripps Research Institute

FDA and NCATS Cure ID for Long COVID
Heather Stone, FDA

Lessons from ACTIV Agent Prioritization
Dr. Timothy G. Buchman, Emory University

RECOVER-TLC Agent Submission Portal
Dr. Stacey Adam, FNIH

Panel Discussion
Moderator: Dr. Sarah Read, NIAID

Panelists: Dr. Julia Moore Vogel, Scripps Research Institute; Heather Stone, FDA; Dr. Timothy G. Buchman, Emory University; Dr. Stacey Adam, FNIH; Dr. Josh Fessel, NCATS; Meighan Stone, Long COVID Campaign

12:30 pm **Lunch**

1:15 pm **RECOVER-TLC Trial Design Challenges**

Populations
Dr. Sally Hodder, West Virginia University

Panel Discussion
Moderator: Dr. Sally Hodder, West Virginia University

Panelists: Angela Meriquez Vazquez, Children's Partnership; Dr. Sharon Saydah, CDC; Dr. Helen Ward, Imperial College

2:00 pm **Study Designs**
Dr. Priscilla Hsue, University of California Los Angeles

Panel Discussion
Moderator: Dr. Dean Follmann, NIAID

Panelists: Dr. Priscilla Hsue, University of California Los Angeles; Dr. Christopher McAleer, AIM Immunotech; Dr. Tom Patterson, University of Texas San Antonio; JD Davids, Strategies for High Impact; Lauren Stiles, Dysautonomia International

2:45 pm **Endpoints**
Dr. Alison K. Cohen, University of California San Fransisco

Panel Discussion
Moderator: Dr. Adrian Hernandez, Duke University

Panelists: Dr. Alison K. Cohen, University of California San Fransisco; Dr. Seth Lederman, Tonix Pharmaceuticals; Dr. Linda Geng, Stanford University; Dr. Todd Davenport, University of the Pacific; Dr. Paul Lee, FDA

3:30 pm **Break**

3:45 pm **RECOVER-TLC Trial Design Challenges (Continued)**

Pediatric trials
Dr. Melissa Stockwell, Columbia University

Panel Discussion
Moderator: Dr. Sindhu Mohandas, Children's Hospital Los Angeles

Panelists: Dr. Melissa Stockwell, Columbia University; Dr. Roberta DeBiasi, Children's National; Dr. Gail Pearson, NHLBI

4:15 pm **Recruitment Challenges**
Dr. Kanecia Zimmermann, Duke University

Panel Discussion
Moderator: Dr. Sally Hodder, West Virginia University

Panelists: Dr. Kanecia Zimmermann, Duke; Dr. Jerry Krishnan, University of Illinois at Chicago; Dr. Catherine Blish, Stanford University

5:00 pm **Adjourn for the Day**

Wednesday, September 25, 2024

How RECOVER-TLC plans to move forward

9:00 am **Recap of Tuesday Highlights including Patient and Provider Input**
Dr. Lindsey Baden, Brigham and Women's Hospital/Harvard University

9:15 am **Regulatory Perspectives**

FDA
Dr. John Farley, FDA

EMA
Dr. Marco Cavaleri, EMA

10:00 am **Break**

10:30 am **Panel Discussion on How Do We Get from Here to the Next Patient-Centered Long COVID Clinical Trials**
Moderator: Dr. John Beigel, NIAID

Panelists: Lisa McCorkell, Patient Led Research; Dr. Laurie Gutmann, Indiana University School of Medicine; Dr. Clint Wright, NINDS; Dr. Yves Rosenberg, NHLBI; Dr. Eldrin Lewis, Stanford University

11:30 am **RECOVER-TLC Next Steps and How to Proceed**
Dr. Jeanne Marrazzo, NIAID

12:00 pm **Adjourn**

Appendix B: Workshop Presenters and Panelists

Stacey Adam, Foundation for National Institutes of Health
Ziyad Al-Aly, U.S. Department of Veterans Affairs/Washington University in St. Louis
Alba Azola, Johns Hopkins University
Lindsey Baden, Brigham and Women's Hospital/Harvard Medical School
John Beigel, National Institute of Allergy and Infectious Diseases
Monica Bertagnolli, National Institutes of Health
Karyn Bishof, COVID-19 Longhauler Advocacy Project
Catherine Blish, Stanford University School of Medicine
Joseph Breen, National Institute of Allergy and Infectious Diseases
Timothy G. Buchman, Emory University School of Medicine
Marco Cavaleri, European Medicines Agency
Alison K. Cohen, University of California, San Francisco
Todd Davenport, University of the Pacific
JD Davids, Strategies for High Impact
Hannah Davis, Patient-Led Research Collaborative
Roberta DeBiasi, Children's National
Steve Deeks, University of California, San Francisco
John Farley, Food and Drug Administration
Liza Fisher, Patient Advocate
Dean Follmann, National Institute of Allergy and Infectious Diseases
Linda Geng, Stanford University School of Medicine
Julie Gerberding, Foundation for National Institutes of Health
Laurie Gutmann, Indiana University School of Medicine
Sally Hodder, West Virginia University
Leora Horwitz, New York University
Adrian Hernandez, Duke University School of Medicine
Priscilla Hsue, University of California, Los Angeles
Joshua Fessel, National Center for Advancing Translational Sciences
Igor J. Koralnik, Northwestern University
Jerry Krishnan, University of Illinois at Chicago
H. Clifford Lane, National Institute of Allergy and Infectious Diseases
Seth Lederman, Tonix Pharmaceuticals
Paul Lee, Food and Drug Administration
Eldrin Lewis, Stanford University School of Medicine
Ian Lipkin, Columbia University
Jeanne Marrazzo, National Institute of Allergy and Infectious Diseases
Christine Maughan, Patient Representative
Christopher McAleer, AIM Immunotech
Lisa McCorkell, Patient Led Research Collaborative
Angela Meriquez Vazquez, Children's Partnership
Sindhu Mohandas, Children's Hospital Los Angeles

Avindra Nath, National Institute of Neurological Disorders and Stroke
Nicolay Nikolov, Food and Drug Administration
Tom Patterson, University of Texas at San Antonio
Gail Pearson, National Heart, Lung, and Blood Institute
Michael Peluso, University of California, San Francisco
Simon Pollett, Henry M. Jackson Foundation for the Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences
Amy Proal, PolyBio Research Foundation
Resia Pretorius, Stellenbosch University
Adrienne Randolph, Harvard Medical School
Sarah Read, National Institute of Allergy and Infectious Diseases
Yves Rosenberg, National Heart, Lung, and Blood Institute
Peter Rowe, Johns Hopkins University
Sharon Saydah, Centers for Disease Control and Prevention
Jaime Seltzer, MEAction Network
Ian Simon, Department of Health and Human Services/Office of the Assistant Secretary for Health
Upinder Singh, Iowa Carver College of Medicine
Serena Spudich, Yale School of Medicine
Melissa Stockwell, Columbia University
Lauren Stiles, Dysautonomia International
Heather Stone, Food and Drug Administration
Meighan Stone, Long COVID Campaign
Paul J. Utz, Stanford University School of Medicine
Mike VanElzakker, Mass General Research Institute/Harvard University
Julia Moore Vogel, Scripps Research
Helen Ward, Imperial College
Clint Wright, National Institute of Neurological Disorders and Stroke
Kanecia Zimmerman, Duke University School of Medicine

Appendix C: Lived Experiences

RECOVER-TLC leadership is dedicated to incorporating voices of those with lived experience during every step of this initiative. As such, anyone was invited to submit a written statement outlining experiences with Long COVID, POTS, ME/CFS, MIS-C, or other related conditions for inclusion in this post-meeting summary. The stories of individuals who opted to share comprise this appendix.

Julie Lam
My name is Julie Lam. I'm a writer who founded MaskTogetherAmerica, a COVID advocacy organization raising awareness since 2020. I am also an immunocompromised Long Hauler.

Through first-hand experience with COVID and working with Long Haulers to share their stories for awareness, I can attest that Long Haulers, struggling with invisible disabilities, want the CDC to promote masking and fix the current guidance to encourage people to stay home when they are still contagious. We cannot rely on pharmaceutical intervention because not everyone can take the boosters or treatments. We need adequate sick leave for the infected to have a better chance for recovery, also not to spread [illness] to others.

This escalating [Long COVID] crisis is increasing absenteeism and disabling working-age people, shrinking the workforce. Long COVID leaves lasting harm to people of all ages, including children.

Before the pandemic, I had a mild form of IgA-Nephropathy. My Long COVID condition is caused by my autoimmune disorder. My kidneys were damaged by a seemingly mild infection, despite being fully vaccinated. In addition, after struggling for over two years, I was also diagnosed with two incurable conditions triggered by COVID-19: Sjögren's Syndrome and Obstructive Sleep Apnea.

In 2021, when Omicron hit, our government kept saying the new strain was mild. Dr. Fauci said families with 2 doses can 'feel good' about gathering for the holidays. But I caught COVID at a Christmas gathering, infected by someone vaccinated and asymptomatic. COVID was nothing like a flu. 5 nights of insomnia. Shortness of breath. I couldn't breathe when I lay down. Burning pain in my back came from my kidneys that were inflamed.

On New Years' Eve, my nephrologist got me a lower dosage of Paxlovid because of my underlying condition, sparing me from hospitalization, while millions died worldwide from this wave.

A couple of months later, while I was driving, I suddenly felt shooting pain in my eyes. The pain forced me to pull over in the middle of traffic in Manhattan. I started to feel very tired every day. My eye [pain] flares up constantly when I work on my computer. I wake up with sore eyes, as if I hadn't slept. Inflammation also gave me joint pain that makes me unable to move properly.

My primary care [doctor] sent me to specialists, including sleep doctors, an ophthalmologist, neurologists, cardiologists, an endocrinologist, a rheumatologist, an orthopedic doctor, and neurosurgeons. I had sleep studies, a nerve test, and many MRIs. Every appointment requires a long wait. I am lucky because my husband's health plan allows me to get diagnosis for each condition— what I need in order to move to the next step.

Is the nightmare over now that I've been diagnosed? I couldn't tolerate the C-pap which was the only treatment for Sleep Apnea. I also reacted adversely to treatments for Sjögren's. My kidney condition progressed from stage 1 to stage 2. One medication to treat IgAN costs over $15,000 a month! Unable to get insurance coverage prompted me to join an experimental medical trial to support science.

Though I'm a vaccine advocate, I cannot get another COVID booster targeting the latest variants.

I share my story today because I know patients like me are getting gaslighted, bounced around in this giant health care maze, lost, exhausted, not being cared for. Most people with Long COVID are undiagnosed. Patients like me are avoiding even cancer screening because of fear of reinfection.

We have been abandoned in the health system.

Anonymous
I am a patient who was infected with COVID in 2020 and have had Long COVID since.

Billy Hanlon
Please prioritize pharmacologic interventions in this next wave of clinical trials as the majority of us have already tried behavioral interventions that were not successful.

Anonymous
I've had Long COVID for 11 months. I thought I was doing better but then got re-infected. I now have early signs of PEM and am horrified of falling into ME/CFS. I'm horrified my life as a young adult male is crumbling toward a chronic life of laying around.

Anonymous
Two years of fatigue, myalgia, brain fog and no longer confident. Getting worse while it's somehow more manageable.

Anonymous
Background: I am 54-year old wife, mother of 2 college kids, electrical engineer, program manager, aspiring 7th grade math teacher who tested positive for COVID Christmas Day 2021. I developed many symptoms including pneumonia (that required 10 months of low dose steroids to minimize ground glass), steroid induced diabetes, asthma, dysautonomia, neurological issues, dizziness, headaches, chronic fatigue (malaise) and pain, tremors, severe leg cramps, Tachycardia, and minimal deep sleep (according to my MUSE headband). I have been going to

treatments and doing apps on my phone almost daily since April 2022 including acupuncture, BrainHQ, CogPT, Continuous positive airway pressure (CPAP - nightly), more than 120 sessions of Cyclic Variations in Adaptive Conditioning™ (CVAC), Lumosity, 35 sessions of MeRT TMS, Mindfulness, neuromuscular massage, 123 sessions of Sonal TMS, physical, speech and vestibular therapies, 18 sessions (2/week for 9 weeks) of pulmonary rehab, RightEye, SMARTFIT. I was evaluated at the Mayo Clinic in Minnesota in January 2023 (tilt test, hearing evaluation). I contracted COVID again in January 2024. Most progress up to that point was negated so I "started over". My medication list includes Cyclobenzaprine, Duloxetine, Gabapentin, Midodrine, Naltrexone, Propranolol and a slew of supplements. My health has been my new job since becoming disabled in March 2022.

Main Point: I developed avascular necrosis in both hips (right hip confirmed in August 2023) and left shoulder. Since the right hip has already begun to collapse and I am having a hip replacement soon. My inflammation markers also remain high.

Question: Is anyone looking at a correlation of inflammation caused by Long COVID and AVN? Note: Some of my specialists have pointed to the steroid use as the main contributor. However, there is one who refutes this since the doses were so low.

Jacey Gomez
JUST FIND A CURE ALREADY.

Anonymous
I've been affected by Long COVID since April 2022 and I'm now 29. I finished my university and started a job. My initial infection was mild and lasted a week, but my life is ruined ever since.

I had to leave my job, I had to cancel my dream of adding my master's degree, I had to move back into my parents' house, I had to stop my sport, I had to stop nearly everything what makes me, me. My life stopped and I'm waiting. I'm waiting and waiting and waiting. I got a bit better and I'm now more or less homebound, I can do some stuff to distract me, but I'm still very limited in my daily life. Everything that lead to becoming better was researched by myself. Not even one doctor brought up something helpful. [Due to doctors not offering much help, I have resorted to seeking aid from non-traditional sources]. Doctors are still questioning the existence of Long COVID/ POTS/ ME/CFS/etc.

I don't know if I will ever be able to work again, I don't know if I will ever be able to start a family, I don't know if I can take care of my parents when they are old and so on. The worst part about this is, not knowing and no one is really taking the actions to clear these things out. 2024 and we are still talking about exercise as a treatment for PEM. PEM deniers are leading trials about ME/CFS etc. It's a freaking nightmare and we are left behind.

Long COVID and COVID in general is a threat to global health and the global economy, yet countries are still debating about yoga and singing as treatments or they don't do anything at all. Just let it rip strategy, I guess.

It is insane to think ignoring Long COVID and COVID, is a proper approach. [redacted] COVID isn't going anywhere, and people are getting sicker and sicker. Sick people can't work. Disabled children can't go to school and won't get a job.

The NIH needs to take this as serious as it is. We need trials with potential drugs, we need biomedical research, and we need it yesterday. Just like HIV in the past this stuff needs proper funding and then there will be solutions. Millions of people around the globe feel abandoned, unseen, and devastated. They need help (proper help and not yoga).

Anonymous
I am a young ME/CFS investigator and seek help for any potential opportunities to support myself in furthering my research in this area. It is an area that is dismissed from typical researchers. Because of the symptomatic nature of ME/CFS and Long COVID, it was so tough to get some researchers and doctors to believe in the symptoms. From my perspectives, this is really related to different personalities and experiences. [Many individuals] are more resilient to trauma and other external stimuli, so they neither have the instinct nor the experience [to empathize with] Long COVID and ME/CFS. This creates roadblocks for researchers to dig deeper into the symptomologies and cannot [lend] any trust to patient reported outcomes. This is a fundamental issue and that leads to many [problems] including [lack of] funding and dismissive attitudes in building solutions. Thus, I would really like to have more mentorship and education programs to provide better understanding of the disease and provide deeper navigation ways to allow people who have not experienced Long COVID to understand their deeper logics of why they cannot sympathize with [individuals living with Long COVID]. Mentorship and funding opportunities for those researchers are fundamental. I have faced so many challenges in doing ME/CFS research in my current lab, and I would say this is far too difficult to transform these principal investigators to put interest in.

Destry Lezotte
I got COVID for the second time at end of September 2023. October 11, I felt dizzy at work. I could not stand for more than a few minutes; that has been my life since that day. My symptoms are POTS symptoms, but my doctors will not diagnose it as POTS. I had to quit my job because of the requirements of standing for half my shift. I am currently unemployed. I waited 6 months to see a neurologist only for him to refer me to another neurologist who could not see me for another 6 months. I volunteered with RECOVER after the pulmonologist referred me finally which is ridiculous because it seemed you could only have a doctor refer you. What if you didn't have the money to see a doctor? My experience with [name redacted for privacy] was good. If [they] need me to be part of more RECOVER trials, I will be happy to do it.

Christine Walter
My first acute case of COVID was confirmed by PCR test on 7/14/2020. Symptoms began 6/27/2020 but I didn't have access to testing [where I live]. Initial symptoms included fever, rigors, sore throat, cough, night sweats, headaches, and muscle aches. Fevers and rigors resolved by end of July 2020, however headaches, muscle aches, cough, sore throats continued. Never hospitalized. Continued to test positive for COVID by PCR biweekly or monthly through

11/10/2020. Tested negative for COVID on 12/11/20. In October 2020, I began to develop mouth and tongue ulcers (which I still develop with too much activity), have episodes of phantosmia (everything smelled like garbage), and have tachycardic episodes. ENT eventually biopsied my tongue ulcers, bx was negative. Medrol dose packs and dexamethasone mouth washes help with mouth ulcers, phantosmia is better now, and I am on Bystolic to control tachy episodes. February, March, and April 2021, I developed urticaria everywhere except hands and face, would last 7-10 days and resolve, then reappear a week later. Cough persisted, pulmonologist diagnosed reactive airway disease and 2 inhalers helped with cough. A second bout of COVID in Feb 2024 exacerbated my PASC symptoms, causing tachy episodes where HR was greater than 200 for 15 minutes and I was referred to a Cardiac EP. I initially sought care with my internist, then at a Post COVID Clinic [location redacted for privacy] where I was diagnosed with Long COVID. I sought care at [another] Post COVID Clinic [located redacted for privacy], was diagnosed with ME/CFS by [name redacted for privacy] in July 2021. I was diagnosed with POTS by [name redacted for privacy] in February 2023. I have been referred, evaluated, and treated by many doctors- IM, Pulmonary, Cardiology, Cardiac EP, Infectious Disease, Sleep, Immunology, Neurology, Endocrinology, ENT, Rheumatology. Prior to contracting COVID in June of 2020, I was in very good health. I jogged about 20 miles per week, participated in cardio and weight classes twice a week. I ran a half marathon with my daughter in April 2020. I am married, have 4 adult children, worked part-time, was in graduate school and was an active volunteer. Because of LC symptoms, I quit my job, and am still taking 1 graduate class at this time. I am lucky to be supported financially by my husband. I cannot exercise. When I have tried, I have spent days in bed recovering. I do restorative yoga and take walks when I'm up to it. My life and activities have become greatly reduced. I need to pace myself with physical, social, and intellectual activities or I relapse, suffering from Post Exertional Malaise. I am 58 years old, and my life has been turned upside down, my activities are limited, and my loss is significant. However, my heart breaks for young people with Long COVID, I cannot imagine their suffering from this in the prime of their lives. More research and a cure are needed, especially for those who are much younger and afflicted with debilitating symptoms of post-viral illnesses.

Sara Nudelman
[I have had] Long COVID for 2.5+ years [where I have experienced] severe brain fog [and being] house/bedbound. Things that have made a marked difference [in my health]:

Peptide SS31 injections: [helped relieve] sound and light sensitivities, dizziness, head pressure and squeezing.

Peptide Cerebrolysin injections: [aided in] elimination of tinnitus, migraines/headaches, dizziness down to 10%, able to walk around without the room spinning, vastly improved word recall, slight improvement in short and long term memory, am now able to have a conversation where comprehension is significantly better, and normalization of hunger cues.

Ipamorelin troches: improved hormone levels and sleep quality.

Plasmalogen replacement therapy: Continued improvement in neuro symptoms.

Nad+ injections: Improvement in energy levels, still house bound but able to sit up more.

Glutathione injections: Again, improvement in energy levels, still housebound but able to sit up more.

I am one of many people who has decided to trial peptide injections because I had zero quality of life. Many of us have posted our experiences online and there are several peptides that have given relief to LC sufferers.

Things that did damage:
Graded exercise: Helped Dysautonomia, caused a severe crash due to PEM. PLEASE STOP TRIALING EXERCISE FOR PEM! YOU ARE HURTING PEOPLE!

John Haughton MD, MS
Five Toes or Ten – a journey through physiatry, life and what works to fix Long COVID.

Includes specific approach for treatment of Long COVID brain fog and fatigue by addressing inflammation and blood flow.

Comments delivered during provider / patient lived experience talks at the Recover-TLC conference on Tuesday 9/24/2024.

I am a geriatric rehab physician who is now clinically working with those affected by Long COVID and ME/CFS.

Affiliation: Medical Director for the Renegade Research, a patient lead non-profit 501c3 working on various interventions, including inducing remissions in those with ME/CFS.

Additionally, I have been a member of the Patient Advisory Committee for the NIH Clinical Center for about 20 years and was treated at NIH as a teenager with bone cancer.

My comments and the paths and treatment approaches discussed here followed from looking for solutions to wound healing and then Long COVID, first personally and then expanded to about a dozen patients treated and with positive outcomes of reversing brain fog and fatigue.

Unfortunately, as a physiatrist, the question of repairable ongoing inflammation and fibrosis vs tissue too far gone comes up all too often, more so in this SARS-CoV-2 era.

With millions post-viral, lots of patients (and medical personnel) are going through an ongoing internal body fight between inflammation and healing: “Long COVID”.

We are learning the issue is small vessel / local hypoxia and associated inflammatory cytokines are driving the action. The spike is wreaking havoc throughout the body.

Why? It turns out that three spikes together fit nearly perfectly into the receptor (TLR4) that normally flares during sepsis and is usually driven by gram negative outer wall Lipopolysaccride

(LPS). The spike sets TLR4 to start inflammation then hypoxia from swelling and microclots continues to drive inflammation.

Finding and starting metformin in 2022 was key for me in trying to stabilize some post fibrotic wound issues in my leg that flare every once in a while. I'm not diabetic, but the anti-inflammatory effectiveness of metformin made sense and studies showing positive cardiac effects were a bonus as I had Adriamycin as a kid. To my surprise, about six weeks later, not only did the skin look better, multi-tasking was easier and I could remember more too.

I realized my forgetfulness and lack of concentration focus wasn't just "getting old". Looking back, the root cause was almost certainly unresolved, ongoing microvascular inflammation – and this was amplified by COVID in the spring of 2020. My work was limited to part day concentration and is now no longer constrained. Productivity is back to levels from 15 years ago.

Treating it with Metformin (500mg) and/or Berberine (500mg), Curcumin (500mg of curcuminoids), Nattokinase (2000-8000units), Probiotics, and pulsed fisetin (3000-4000mg once a month over 2-5 days) has worked for me and helped a number of others reverse brain fog and alleviate fatigue post COVID. Not a magic wand but is available now and follows the science and can be used now while we wait for definitive studies of the "right" cocktail of treatment.

Anonymous
The TL/DR version is now I have PEM, fatigue, brain fog, impatience, muscle wasting plus exercise intolerance, my senses of smell and taste have been broken. I apparently have brain lesions that may or may not have been caused by COVID and have had the classification of 'Mild Cognitive Impairment' applied. If the testing is correct, I lost about 30 IQ points. My D-Dimer is consistently elevated, noting clotting somewhere.

I am participating in studies and a clinical trial, which I hope will help others. The studies have helped me get referrals to specialists my insurance would never have approved without 'proof.' I AM thankful for that.

I first contracted COVID in November 2020, confirmed by an official test conducted by my state's department of Health. [I was] reinfected July 2023 (mild). [I received] three rounds of vaccinations.

My 2020 [acute COVID] case appears to have been relatively mild compared with other instances, including an uncle who died in December of that year, alone in the ICU. I had a persistent 101-degree fever, teeth crushing and shaking chills, horrible headaches, and extreme fatigue. There was no treatment I knew of at that time. I was not about to venture out to a hospital due to the overcapacity, excess wait times, and death tolls. I treated myself with massive Vitamin A and D dosing, Vitamin C, zinc, breathing exercises, and of course lots of sleeping. [I] slept for days.

The illness was primarily centered in my head, it never really went to the lungs, although I did have some chest tightness, thus the breathing exercises. My senses of taste and smell disappeared, however those particular [symptoms] always occurred when I got a cold, so I thought I had a really bad cold or flu until the COVID test message came back to me.

During the illness run, I had olfactory hallucinations--very specific smells from my childhood that absolutely could not occur in my current living arrangement. I have not heard this from others, and when I tell the COVID researchers, they get rather confused looks on their faces. These 'smells' occurred although I really couldn't smell anything else. Smell and taste were gone for a long time, and now they come and go, nowhere near as refined as I remember. Sometimes I can taste but not smell, smell but not taste. I now smell 'chemicals' in all sorts of products, instead of whatever their intended fragrance is. It is always the same chemical smell. I smell it in perfumes, shampoo, conditioner, laundry products, soap, skin care products. Coffee smells great but doesn't taste like coffee. Chocolate tastes fruity, and I usually don't purchase 'fruity' chocolates (prefer 80+ cacao). So many other examples, but I will bore myself and must move on. Subsequent sniff tests have me missing up to 25% of the smells, although that is getting a bit better.

I kept trying to work, that didn't go well. I used to joke with my coworkers that I had [a short] attention span. COVID made it worse. I had the good fortune of having been a federal employee for over 30 years and had met the time in service and age requirements to retire right before I contracted COVID. I retired June 30, 2021, and slept for a year. I have not tried to get a job, especially in my field, since. I might have the mental presence to water plants at the local nursery.

I am now more impatient with basically everything in my life, and much quicker to get upset about it. But when I try to concentrate it makes me tired. I couldn't read a book or newspaper for about two years, and I used to be a voracious reader.

Mild exercise [makes my body] hurt the next day to week, depending on what I did. I feel as if my muscles are wasting away, and I am getting weaker. Hoping for more testing and treatment.

Anonymous

One of the most frustrating aspects of living with LC is precisely this invisibility of it all. Despite having personally documented over 22 different symptoms that have manifested since I started noticing that something was off in the spring of 2022, 99% of the time I appear “normal” to those who see me. This is partially due to the fact that many of the symptoms I’ve had are indeed invisible on the outside. But it’s also partially due to the fact that I’ve almost wholly removed myself from public interactions with people, and that I don’t post pictures of me lying in bed, me using my cane, me crying, me gasping for air, me losing my sight temporarily.

I was known as someone who traveled the world, hiked volcanoes, went skydiving, danced all night, said yes to adventures. I think it’s hard for a lot of those who know me to reckon with this new version of me who says that she’s exhausted and worn out and can’t think clearly but

doesn't appear to show any issues outwardly. But what do I have to do to prove these symptoms? How does one "prove" that they feel like they are gradually developing dementia-like symptoms? How does one "prove" that their brain fog is so thick, they can't recall words or memories, or even synthesize or comprehend information that's being told to them?

For most of the last 2 years, all my lab results would come back normal. But I felt crazy inside. Doctors told me it was nothing, it's not real, they had no answers for me. My own family asked me if I was faking it. The gaslighting from my family, friends, doctors, and society has been unimaginable.

Some symptoms I've documented over the past two years include: brain fog & memory loss, changes in speech, temporary loss of vision, severe fatigue/tiredness, PEM, mental fatigue, headaches and migraines, dizziness when standing up, racing heart rate, increased depression and anxiety, sleeping disturbances, bruising, inability to regulate body temperature, temperature dysregulation, abnormal chest pressure; shortness of breath (despite not moving), changes in menstrual cycles loss of appetite, hair loss.

I try my best to wear a mask now every time I'm in any kind of public/crowded space. I hate wearing masks. I didn't ask to be part of this club. But I know that being immunocompromised doesn't really give me a choice. COVID is airborne. We now also have mpox and bird flu. Why would I risk getting sicker than I already am? I'm sad to admit that I truly wasn't thinking about my community and others who have been excluded from community spaces because people like me didn't mask to make spaces more accessible to all. It took me getting disabled to finally realize this.

I often get stares or questions when I wear a mask. The peer pressure not to wear a mask is unreal. Though I haven't been yelled at or spit on or coughed on (yet), I have heard of so many stories of such occurrences, and every time that I leave my house masked, I brace myself for that to be the day. The mental fatigue of bracing to be assaulted or harassed wears you down.

It's been the loneliest two plus years of my life, especially as I watch my own body and mind's slow descent into atrophy and chaos.

Jennifer Danielle Gillan
My experience has been alienating from day 1. I have been impacted since September 2020. Sent home from the emergency room to manage my infection at home because I couldn't breathe. Too sick to seek care, too confused to understand or explain what was happening to me. Specialists were difficult to see. They lack information and empathy. Insurance refused to cover diagnostic exams and decided I needed a cardiac cath. It took two years to be cared for finally. I was treated at Mayo in their PRC program for central sensitization. I was treated at Aviv with HBOT.

The game changers were diet, the whoop to manage pacing and collect data on interventions, PRC treatment, HBOT, Lactate Testing, Zone 2 training, Pilates and LDN.

[Long COVID is] a polarized illness that is difficult to live with and manage with the lack of education and awareness in the healthcare community. ME/CFS resources have aided in my discovery of self-care and evidence-based treatments. We all have suffered enough, and there are things that can be done to support and protect us. Mask bans and repeated exposures destroy the quality of our lives and limit our potential to be independent and successful.

Wearable data is essential to evaluate and create data for the patients at home to avoid pushing and crashing. Together, we can do better!! We need data and metrics to measure our trends over time to improve our treatment and recovery.

It has been horrible I have only been able to advocate for myself because of my pediatric background in oncology and bone marrow transplant.

We need a definition and guidelines to be treated.

Michaela Martinez
I began suffering from LC January 2022 with the primary symptom being cough and shortness of breath. I was unable to reach in front of me to grab a water bottle off the table, unable to change positions in the bed, unable to take a shower alone, and limited to a small area of living with all necessities brought close to me. Any form of exertion was too much for me for many months. I have spent the past 2.5 years escalating asthma medication (I am now on 3 inhaled corticosteroids, Tezspire, allergy medication, and daily steroids) with minimal relief of my symptoms but still happy with any improvement I received. It was not until I found a doctor who has his own personal experience with LC that truly cared for his patients that I found some light in my LC journey. He put me on Lexapro and eventually Low Dose Naltrexone and between both of those, I can now fool a stranger in my abilities due to not noticeably gasping for air and coughing. It is so important for our healthcare community to understand that imaging and tests are not the guidance for treatment for those with LC. Listening to the patient and trying new things is the only thing that helped me. My asthma doctor never treated me based off my PFT, he treated me based off the loss of quality of life and ability to function with even minimal ADLs. His increase in my medication gave me 20-30% of my ability back that no other doctor was willing to help with. I was frustrated many times leaving a doctor's office being told " Long COVID is difficult to deal with and I am sorry you have it" and no recommendations or empathy behind the statement. I would rather be told by a physician that they do not have the answer but will reach out to colleagues for ideas than be left to think that I am alone and crazy for the way I feel.

I now partner with a physician in Northern Colorado to offer a Long COVID Information, Discussion, and Support group to those who suffer or care for someone with Long COVID. Facilitating this group has brought so much hope and help to our community. Even when our discussion [group] for the night does not have the answers they want, they feel educated, valued, and supported by the opportunity to join with a community who understands them and cares for their wellbeing. We need more funding for support like this. The physician and I are currently operating without a budget and volunteering our time to these participants but

quickly becoming overwhelmed with the manpower needed to run even a simple group and connect with the 200+ contacts we have gained in 6 months.

Amy Hackley
PEM, post exertional malaise, used to be a symptom that was unique to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Long COVID patients with PEM should be evaluated for ME/CFS and/or identified as an unique LC subtype. I highly suggest that ME/CFS research experts be consulted or ideally added as researchers for future studies. There is a wealth of information and experience that could help research into Long COVID for those with PEM.

Dale R. Buisman, NNPe
My Name is Dale Ray Buisman. I am submitting my life journey Long COVID.

I would like to thank you for being willing to listen to my story. I will begin with who I was before Long COVID, my history with the disorder, including many of my symptoms and attempted treatments, and conclude with what today looks like for me.

I am now 65 years of age. Christian, husband for 39 years, father and grandfather. Each one of those aspects of my being has been completely altered [by Long COVID]. I am no longer able to practice as a Neonatal Nurse Practitioner. I first started caring for newborns in 1979 as a Hospital Corpsman in the Navy. I had been deployed with a Marine Corps unit in Asia and was transferred to California in 1979. I requested duty at the Naval Hospital at Camp Pendelton. That was granted, I was moved around between various floors as well as temporary transfers to various Marine Corps units. It was in the summer of 1979; I was temporarily assigned to the newborn nursery that day. The first half of the day I was scared and nervous. The last half of the day I had an idea of what I may need to explore for my future. One day as I was feeding a gorgeous one-day old girl, our eyes locked. Others gathered around to observe the connection. The mutual adoration I think we experienced over the next three days changed my life. I now knew I would pursue a career in Neonatal Nursing.

My first pre nursing class was an English course taken in 1980. I attended many different educational programs over the years. Gaining knowledge, certificates, permits, licenses and various degrees along the way. I took my final college course in 2000. All the while working in various roles in the Newborn Nurseries and Newborn Intensive Care Units. I never ceased building upon my base and gaining new knowledge along the way.

The role of a Neonatal Nurse Practitioner is not a very common occupation that is seen in everyday life. Some of my responsibilities included but are not limited to:

Serving as the primary caregiver to newborn infants in the NICU.

Assessing, diagnosing, and carrying out procedures in the care of at-risk newborn infants.

Designing treatment plans for infants with complex health issues.

Prescribing medication.

Educating and supporting parents and guardians in the care of their newborn infants.

Ordering and performing medical tests and procedures.

Lead a team in neonatal resuscitation in the delivery room and in the NICU.

An abbreviated version of my journey now follows.

12/23/2020 I received, very hesitantly, my first injection of a poorly tested injection advertised to prevent SARS-CoV-2 infection. Prior to this and in the ensuing months I was exposed every day on the job [as a neonatal nurse practitioner]. Usually, the exposure was from a laboring mother who had no idea that they were positive for the virus. They were symptom free. [Between 09/27/2021 and 12/31/2021,] I had an annual physical and all was great. I developed COVID-19 symptoms and tested as COVID positive. I was off work ill [for a month]. I was back to work [for two months]. New viral symptoms [developed], and I tested negative for COVID and influenza A and B. I last worked on 12/25/2021. Long Term COVID changed my life.

As you have heard from everyone; the symptoms vary from person to person and time to time. I will delineate an abbreviated itemized list of difficulties I have faced over the last few years: Fatigue, fever, chills, weakness, post-exertional malaise, cognitive dysfunction, memory impairment, speech/language difficulty, sleep disorders, headaches, depression, taste and smell only recovered to about 40%, hallucinations, tremors internal and external, heart rate fluctuations, palpitations, hypertension and hypotension, and pain/burning in the chest, itchiness, rashes, loss of all leg and axillary hair, most chest hair and much of my scalp, GI upset, and appetite-related symptoms, shortness of breath, worsening of tinnitus, loss of hearing, several vision changes requiring new prescription glasses, eye pain, nasal irritation, burning, congestion, recurring epistaxis, decrease in penile size, ED, loss of ejaculation, new and heightened immune responses, total body muscle and joint pain. As you are aware, the list can go on and on. The [symptoms] vary over time, being unpredictable.

My list of providers is enormous. The number of treatments I have spent money on is ridiculous. The vast majority of them seem to provide little or no improvement and some have exacerbated the problem. Hyperbaric Oxygen Therapy was supposed to improve a number of symptoms. Instead, it made all of them worse and thoughts of suicide were with me all the time for months. Magnetic impulses for depression, made it much worse and now [I suffer from] long-lasting headaches.

I have regressed from a provider to someone who cannot even sort out his own medications. I have lost the trust of my family for any decisions. I have lost more than $250,000 trying to find solutions in addition to what health insurance has covered. I rarely drive. I am not permitted to even try to take a vacation to get away from it all and sit on a beach because again I am not trusted to make even the simplest decisions like when and what to eat. Now that it is all down

on paper, no wonder ending it all looks like a feasible alternative to the pain and suffering I endure and am causing my loved ones.

My life has been forever altered; I lost my career prematurely. What a coincidence in light of the fact that my career was providing care to the premature and infirm babies in the various places I practiced. Physically: My abilities and my disabilities tend to change on a weekly basis. I have learned to adapt to whatever organ system is misbehaving on a specific day of week. Mentally: I live with Moderate Depression, with the ebbs and flows of improvement and worsening that can change even during the day. Cognitively: I [am] amazed at what I think I see in ability to solve problems, follow instructions, carry out simple tasks. And it seems to continue to deteriorate with time. Spiritually: My bright spot. Yes, this aspect has had ups and downs as well, but generally speaking, I see myself on the correct trajectory. Always looking for areas of improvement.

I have been suspicious of government for the last 3 decades. My eyes have been opened wider to the power that is there and how terribly it can and has been abused during all of this. I have been a real proponent of the large pharmaceutical companies and the way they are able to do good for the world with all the research and advances in treatments. But I sure have lost faith in them now. I see them as power and money hungry, not looking out [for] what is best for the customer.

Finally, I will be ok. I will likely never be as strong as I once was though I will continue to try to regain some strength. Mentally, I have learned many tools to assist me from falling too deeply and to pick myself up when I feel like, or it is pointed out that I am diminishing. Cognitively, I will enjoy learning more as I am able but being aware I will never be the same. Spiritually, I am determined to grow deeper and deeper in my faith and help those along the way that are interested.

All in all, I have had a blessed life. If the end be today, so be it. If I am [un]able to watch my grandchildren grow up, so be it. I strive to accept where I am each day.

Thank you for reading.

Caroline Kern
I am in the RECOVER 4 year study at Mt Sinai (since 2022), and also the RECOVER-Vital (Paxlovid Study) through UPMC. I have been absolutely appalled at the lack of masking at pretty much all of the appointments I have been to over the years. When there has been masking, it is not with KN95s and they are put on once I am already in the room, or people ask me if they should put one on—putting the onus on me. This includes people coming in to pull blood. I had a study coordinator wearing one of those neoprene masks for our appointments, when even in 2020 those were determined that they were completely ineffective. I finally said something to him, and he wore a better mask the next time, but still, why should I educate RECOVER staff/or study personal on proper masks or masking policies for a high risk population already dealing with major health problems from COVID?

For someone who generally has a good attitude with medical appointments, despite my poor health, it has been hard to go to a study for a condition, caused by a virus that is still very much circulating and have to go to medical buildings where there are zero masking policies. I already can't work as much as before, so every appointment is 100% risky. Optics alone, it also doesn't help if people researching and caring for LC patients do not also mask themselves. It is part of the larger dissonance around COVID and the pandemic—acting like it was a thing of the past, that people shouldn't worry about, though you all are the ones seeing the most devastating effects in real time.

The 4 year RECOVER study has been one of the most futile studies I have been in and I hope that over the years, RECOVER can better work with ME/CFS researchers to inform better study design and approaches. I have diligently gone to all appointments, given so much blood, urine, feces, and time going to other appointments for a nominal amount of money because I am able bodied enough and the data is important for the research.

Being taxed on the RECOVER-VITAL study like I am a freelancer (30% of the total money will be taken for taxes) is absolutely ridiculous. I freelance for work (when I can work now) and do write offs for that. I took Paxlovid for 15 days and it was a horrible experience all around, before I took the placebo—it was so noticeably different in symptoms/taste in the mouth/ability to drink coffee that is how I know it was the placebo in part two. I had to adjust my meds and some I couldn't take at all. It was a very difficult time and in the middle of it, the Stanford study came out that Paxlovid didn't help at all. I still finished up because like I keep saying, the research is needed.

Point is: unlike actual freelance work that I bill hours, do write offs, etc, doing a drug study should not be taxed in the same manner. My life was affected 24 hours a day and what are the write offs for that? This is a side rant, but the money is also not good enough to make any of these studies worthwhile. Again, I actually believe in research and also desperately want to access to any treatment that might help, so I volunteer for those reasons. I was asked by so many people why I would do these studies for barely any money at all and half-baked solutions and the answer is cause the data is needed and I am determined to get to a better spot with my health.

I know that I will not be the person I was before, and I have had to give up so much in my life from this illness. I had to have a heart procedure due to LC at age 42, when I was in good health prior to getting COVID. I have had 4 stellate ganglion nerve blocks and out of everything that I have tried, those have put the biggest dent into my symptoms (after the heart procedure stopped the SVT runs). I have tried countless meds, been a patient at two different LC clinics, tried every doctor that I can get a referral for, and am in medical debt for it all. So, when I complain about masking, this is what informs all of this. Please do better.

Jermaine Greaves
I was born with cerebral palsy and developed a chronic illness 3 years ago. I have also had COVID twice. My experience with disabilities has shaped my world views. While having a chronic illness and COVID, three years ago I was bed bound unable to work. I [relied on] a

fundraiser for my rehab and housing care during this time. As I navigate COVID and my chronic illness and disability symptoms, I have to get creative with how I pay my bills. [I have used] gofundme, spotfund, and crowdfund online. I'm currently $12,000 behind on rent and I'm worried about homelessness and [un]employment. COVID and chronic illnesses are disabilities [and we who suffer from them deserve] rights. I want better for us as a disabled community. COVID for me caused breathing problems and I was bedbound. As people with disabilities, we deserve rest, but society has not [enabled] us [to do so].

Rivka Solomon
Hi, I'm Rivka Solomon. When I was 21, in 1983, I got infectious mononucleosis from the Epstein Bar Virus. I was so sick for a full year; I could barely stand up to brush my teeth.

After a year, I experienced a "semi-remission." But then I got a second infection, pneumonia, and this time I stayed sick for good.

For decades now, I've been in or near my bed. I was diagnosed with ME (also known as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome).

Before the pandemic, there were 2.5 million in the US with ME; 24 million around the globe.

Because no one took ME seriously, it got (and still gets!) little research funding. As a result, I can't access a single FDA approved treatment for my disease -- because there are none.

In 2020, when a viral pandemic hit, I feared we'd see millions of *new* people with a post-viral illness like mine. And we did: about 50% of those with Long COVID are eligible for a diagnosis of ME.

Personally, for me, at the start of the pandemic, I got a presumed case of COVID, before there was testing available. Ever since then, my stomach has been burning. It's been awful. And research shows GI problems are not uncommon in Long COVID.

Since my presumed COVID infection, I've also been weaker and sicker than my usual. With all that, my doctor gave me a Long COVID diagnosis -- which comes on top of my ME diagnosis.

There are millions of us who had a pre-existing infection-associated chronic illness -- such as ME, chronic Lyme, POTS, or dysautonomia -- who then got COVID, and are now, like me, even sicker. We have the same symptoms we had prior to COVID, only worse. Or we have new symptoms, as I do with my burning stomach.

So, do we have Long COVID -- or is our original illness just worse? Who knows because there's no funding to study that.

There's one hopeful thing coming out of this pandemic: Advocates from these various infection-associated chronic illness communities are now working as a coalition.

A key goal of ours is to get NIH to study these neglected illnesses together -- from ME/CFS to Long COVID to dysautonomia to chronic Lyme, and more. Instead of what we have now -- separate silos at NIH, where each illnesses get isolated (and underfunded) -- we want NIH to establish a new office on infection-associated chronic conditions and illnesses. This way, research on our diseases could be more coordinated and cost-effective. After all, many of our symptoms are similar. And many of us have each other's illnesses as co-morbid conditions.

So, 4 years after I got my presumed COVID [diagnosis] -- and 4 decades after I first got ME -- yes, I'm still stuck in, or near, my bed much of the time. But now I'm working with a beautiful coalition of advocates hoping to change the way ALL these infection-associated chronic illnesses are researched and treated.

I hope you'll help us.

Anonymous
I have had Long COVID since January of 2020. By January of 2021, I was no longer able to work due to constant exhaustion and cognitive issues so severe that I lost 60 points on the IQ test. I thought I had early dementia. SSDI Disability was approved in 2024. Before COVID, I was working full-time, married, debt free, and building for retirement. I exercised vigorously 3-7 times a week and was in good shape, 40 pounds lighter. Since January of 2020, I have lost my job, my health insurance, my marriage, my health itself, all of my savings, most of my investments, the ability to exercise, many of my friends, and my quality of life. In 2023 alone, I spent $15,000 out of pocket on medical expenses trying to figure out what was wrong with me and how to fix it. I am tens of thousands in credit card debt from living expenses over the years and the disability payments I receive now do not cover my mortgage and utilities. Diagnoses from BEFORE COVID infection include Autism, asthma, IBS, Migraines, Seasonal Affective Disorder, and Hypovitaminosis D. Diagnoses from AFTER include ME/CFS, POTS, MCAS, Fibromyalgia, Raynaud's, NAFLD, hypoglycemia, hyperlipidemia, mitral valve regurgitation, first ventricular tachycardia and now bradycardia, gastroparesis, methane-dominant SIBO, costochronditis, and obesity (I have gained 40 pounds from Long COVID). Other findings include sky-high D-Dimer, impaired pulmonary function tests, and small fiber neuropathy. I have struggled with suicidality for years now. Most recently, I found out that I have Beri Beri. I have done and will continue to do everything possible to recover, regain my quality of life, and be able to work again.

One thing that has given me hope is being able to be a participant in the RECOVER study, which I joined in 2022. I have learned so much just from which tests they give me, and the researchers are unfailingly kind and encouraging. I'm glad NIH is giving Long COVID the serious attention it deserves. I am also grateful to be alive because there have been several times over the past 5 years that I almost did not make it. On a day-to-day basis, I struggle to eat enough food, drink enough water, and stay out of bed as much as I'm able. I would like to be able to recover enough to have a more meaningful life.

Amy E. Mitchell
I have primary immune deficiencies CVID and APS1, making me particularly vulnerable to

infections. I was first infected with COVID on March 3, 2020. My initial illness lasted 4 months, but it never ended. I developed Long COVID. Within the first month, I had new onset vasculitis, POTS, neuropathy, reactivated Lyme, and lymphocytopenia. Allergic reactions, diarrhea and malabsorption, autoimmunity, cognitive impairment, muscle wasting, anemia, insomnia, and unending shingles came later.

At first, doctors didn't believe me when I didn't get better, but over the years and 7 infections later, they now compare my condition to HIV. My immune system has never been the same. I have low T and B cells. My T cells no longer respond to antigens. I have to remain on antibiotics, antivirals, and antifungals to keep infections under control. Immunoglobulin isn't enough. I catch new infections easily. I have experienced AIDS-defining illnesses: chronic disseminated zoster lesions, esophageal thrush, and muscle wasting. Spike protein from SARS-COV-2 has been detected in my blood, likely from viral reservoirs. And after my 7th COVID infection, caught while at medical appointments, I have tested positive for over 6 months.

My doctors suspect I have a chronic SARS-COV2 infection but have no way to treat it. There are no antivirals or monoclonal antibodies approved for long-term use on COVID. My insurance won't cover more than 5 days of Paxlovid twice a year, nor will they cover monoclonal antibodies because of their EUA approval. I rebound after a single course of Paxlovid. 3 days of Remdesivir failed. I need better antiviral treatment options, as a person with Long COVID, chronic SARS-COV-2, and both genetic immune deficiency and acquired immune deficiency CoV-AIDS. I have resorted to trying off-label HIV medications and herbal supplements. I experience some improvement, but none so strongly as Paxlovid, Evusheld in 2022, or random batches of immunoglobulin due to better matched antibodies. I have no way of knowing how effective these medications are without a way to measure viral load.

Unlike people with HIV, people with long COVID have no tests to prove their chronic infection or viral load over time. The root cause of Long COVID is COVID, SARS-COV2; we need to test and treat for it. And to protect patients, respirator masks need to be worn in all research and medical settings. The last remaining COVID emergency standards set to expire in December need to be extended and expanded to include Long COVID: telehealth, coverage of antivirals and monoclonal antibodies needs to be required by insurance, and the EUA FDA approval process needs to be available for new treatments to incentivize their development and make them available to patients.

Kevin Fogard

In June, 2022 I tested positive for COVID. My symptoms at the time were mild. I went to Urgent Care to confirm that I was positive. At the time, the current thought was Paxlovid could cause a rebound of symptoms. I was in good shape for my age of 68 years. I exercised regularly and had completed 13 marathons for which I continued to train. Due to the mild symptoms and my present state of health, it was suggested that I forego Paxlovid to which I agreed.

Approximately one week after testing positive and while on a walk, I was ascending a neighborhood street with a moderate grade when I experienced a sensation that I had never

experienced before. I became extremely weak and felt completely out of gas. I made it home with a very slow and labored gait.

What I experienced going forward was an approximate two-year battle of a multitude of symptoms that waxed and waned. It seemed as if some entity was marching through the various systems in my body. If I was to list the variety of symptoms that I experienced, it would include: extreme fatigue, post exertional malaise following physical or mental activity, decreased exercise tolerance, palpitations and wide variations in heart rate and blood pressure, sleep problems, difficulty with memory, focus, and concentration, headaches, lightheadedness, dizziness, blurry vision.

SLEEP: The most disturbing symptom that I experienced early on was a racing heart rate associated with sleeping. Whether it be a nap or during the night, I would awaken with my heart racing. For a period of time, it presented every time that I woke up. How do you get restorative sleep or look forward to sleeping knowing you'll awaken with this disturbing fright? It became a vicious cycle of lack of sleep and eventually the anxiety and worry in anticipation of these symptoms.

FATIGUE & ACTIVITY INTOLERANCE: My pre-COVID routine was to exercise daily with different combinations of walking, jogging, stationary bike, swimming, strength training and various other activities. During Long COVID I had to approach my exercise and activities with caution. I had to "stay within my energy envelope" as described in the UC Davis Long COVID clinic guide (1). If I exceeded my energy envelope, I would become so fatigued that attempting to carry out even the most basic activities would be difficult. Quite often the most energy I could muster would be to slowly "PACE" or walk slowly up and down the hallway followed by needed rest. This would repeat many times during the course of a day.

During Long COVID I had groceries delivered to my home because I could not go to the store and often it would be a struggle just to get the bags of groceries into the house. I recall times when I would take an item out of the grocery bag, put it away and then have to sit to gather the energy before I could get the next item. It made for a pretty long session of unloading groceries. I struggled to unload the dishwasher or stand at my sink to shave or brush my teeth and had to lean on the counter because I felt my legs would not hold me up.

CHEST PAIN: On one occasion I experienced significant chest pain which was accompanied by chest pressure, sweating and rapid heart rate. I went to the emergency room due to the symptoms I was experiencing with the concern that I was having a heart attack. I was in the emergency room for approximately eight hours, had many tests and fortunately everything checked out OK.

BRAIN FOG & COGNITIVE IMPAIRMENT: Brain fog presented in approximately the 6th month and lasted quite a long time. I experienced concentration problems, headaches, processing speed issues, poor recall, and just overall mental fatigue. I would sit in the backyard and look out to a beautiful pool, grass and trees and yet feeling completely detached - my environment just did not seem clear.

My GI system was all out of sorts, and I had diarrhea for many weeks.

My skin would intermittently feel extremely warm or hot & associated with sweating.

ANXIETY: As time went on, unexpectedly, I experienced ANXIETY. I became aware that I was afraid of so many things - going outside or even taking a short walk down the block in fear that something would happen when I was out there. These were the same streets that I would jog endlessly while training for marathons and other runs. When I went to the store, I was anxious and felt very uncomfortable standing in a line. I would go shopping early, buy a few items and felt the need to exit the store quickly.

I now realized I couldn't go to gatherings or travel, go to ball games or crowded races, restaurants, weddings, or parties. I felt isolated and my freedom and entire life as I knew it had changed. I was very concerned for the future and my participation in it.

So, I decided I had to do something. I had to come up with a plan to slowly progress and confront the myriad of issues I was facing. Knowing full well that this would not be linear and that energy envelopes are not clearly defined and more than likely would vary from day to day or perhaps hour to hour. The challenge being that COVID was new, I could not necessarily count on COVID research to provide a guide or a path of recovery. Well-meaning and helpful professionals, groups and specialists just did not have the answers being that research and clinical insights regarding Long COVID were in its infancy. So, I jumped in and put together a loose plan to progress.

PLAN: First off, I made appointments with all the appropriate providers depending upon which symptoms were presenting. Over time this included: primary care, dermatology, cardiology, optometry, emergency medicine, social work, Long COVID specialty clinic at UC Davis Department of Pulmonology.

For a period of time early on when I was extremely fatigued, my wife would come home from work and drive me to a local lake to see nature and attempt short walks. Initially the walking distance was limited to a slow walk around the truck with a walking stick and gradually increasing time and distance as tolerated.

I continued with daily exercise as tolerated and monitored all on my Apple watch. PACING, or slow walking was my regular strategy. I ventured outside more and started to explore my physical limits of purposeful walking and eventually started to slowly jog again. I signed up for virtual run/walk/bike events through an online registration platform called Run Sign Up. I entered a virtual race "2022 miles in 2022" that provided an opportunity for me to document daily exercise activity, duration, and distance. Upon completion you got a medal and a shirt just like the community races but competing solo in and around my home and neighborhood. The accountability to the documentation was a key factor in performing consistent exercise even when some of the day's activities were only slowly pacing up and down the hallway. And, when you entered your times and distances you were able to compare yourself to the many others who were also participating.

I used a meditation app by HEADSPACE and participated in daily guided meditation. I entered daily writings in a book titled "365 Days of Gratitude Journal". I monitored my O2 sats, blood pressure and heart rate daily. I participated virtually as a subject in a Long COVID research study through the University of California at Davis with the title: A Study of Positive Emotion Intervention for the Treatment of Long COVID-19 Symptoms.

I played brain games from apps such as Brain HQ. I read numerous books, initially books on Cognitive Behavioral Therapy. I listened to many Audible books. I cooked, followed recipes, and resumed housework as tolerated. I kept up on bills and daily email so as not to lose touch with my daily responsibilities. I kept in contact with family and friends by phone, email, or text.

I texted family members daily using the sharing of cooking, daily meal planning and food preparation as the vehicle and topic for discussion.

Once I started to feel better, I embarked on a progressive plan to experience the outdoors and more normal mainstream social activities. My wife and I planned a series of progressively longer and more challenging drives and eventually trips with overnight camping or hotel stay. Unfortunately, these activities were still carried out with a safety net of wearing a mask, and with only my wife and I participating. We eventually started meeting with other family members or friends outside and in small groups.

My most challenging goal was to attend a yearly fishing trip to Colorado with a few friends. We met yearly for many years but stopped due to COVID. During my Long COVID, the friends resumed participation resulting in me missing two years of the coveted trip and feeling sad and disconnected. Pictures sent to me by my friends were desired and welcomed; however, resulted in a feeling of loss. This year I made the trip - driving over 2000 miles and navigating the activities of the outdoors at Colorado elevations with much success.

It has taken approximately two years to reach the point where I felt a reasonable semblance of my past life. I do not currently experience the severe fatigue that I experienced early on. Any fatigue I feel now is perhaps the normal fatigue of a now 70-year-old man who exercises and performs many activities of daily living and outdoor activities. The brain fog has for the most part cleared, and I see and participate in my environment with more clarity. I am now able to exercise and run/walk with progressively improving strength and endurance. My long walk/run presently is 10 miles with a goal to reach a half marathon distance (13.1 miles) by the end of the year.

The challenge going forward is how to live my life in the manner I have been accustomed to. The ability to travel, gather in groups, attend athletic and social events like weddings and family Christmas parties, or even just going out to dinner poses a concerning risk. How does one navigate the world now with the ever-present chance of catching COVID again? Would I experience Long COVID again, and if I did, what would that mean to my health now that I am 70 years old?

I understand and appreciate the myriad and complexity of experiences that are part of the long COVID landscape. After watching and virtually attending the RECOVER Treating Long COVID - Navigating the Pathway Forward [workshop], I am humbled by the challenges of other Long COVID individuals. I do understand that their story, and perhaps mine, is not yet written in terms of future Long COVID outcomes. To date, I am doing very well. My hope is that science, medicine and organizations like NIH and the RECOVER Initiative will provide the vehicle for research, clinical and experiential insights in order that I and others with Long COVID can continue to improve and move forward in a successful and informed way.

"Longhaulers' Wheel of Recovery: A COVID Survivors Guide". By Robin TImm, Ph.D. & Joseph Henrich, M.A. U.C. Davis Health Services. Department of Physical Medicine & Rehabilitation. Neuropsychology (2021).

Michelle Markoff

I once envisioned a long, healthy life, perhaps even reaching the age of 90. Known in my community for my vitality, I have climbed 14ers and exercised weekly. I didn't smoke, didn't drink, valued my fruits and veggies and often skipped my annual physicals because I didn't have any pressing health issues at the time. Graduating Magna Cum Laude from Colorado State University, I built a successful career in New York from the ground up, later continuing that journey in Hong Kong, where I also started a family. Eventually, my husband and I returned to the United States so our two children could bond with their grandparents.

Never did I imagine or have any indication that a COVID-19 illness would alter my life in such a profound way. In 2020, we took every precaution—avoiding indoor gatherings, wearing masks at the grocery store, even sanitizing our groceries for a time. Then, one September morning, our family woke with runny noses, head congestion, sore throats, coughs, and headaches. My daughter tested positive for COVID-19 via PCR, while my son, husband, and I exhibited similar symptoms but tested negative on different days After three weeks of quarantine, we all began to feel better. However, about four weeks after my initial symptoms, I developed unexpected chest pain—a sensation I had never experienced before. This pain was constant, centered in my chest, and [remained] unchanging with deep breaths. Concerned, my doctor ordered an Echo Stress test after noting an abnormal ECG showing inverted T waves and signs of anterior ischemia. In years past, I had a record of a normal ECG, and this new finding was unsettling.

In November, we took a calculated risk and allowed my husband's brother's family to visit. They were the first guests we welcomed into our home since February 2020. My brother-in-law, a pilot, had driven to reduce any risk of exposure. Unfortunately, on 1st full day of their stay, he began feeling unwell. Days later, we learned that he, along with his wife and child, had contracted COVID-19. Once they recovered and returned home, a tidal wave of sickness struck me.

On November 13, 2020, I stood in my bathroom and spritzed a puff of Chloe perfume in front of my nose, only to find I couldn't smell a thing. Panic set in as I rushed to the kitchen, only to discover that I could taste nothing. That evening, I experienced explosive diarrhea. I had felt a bit fatigued the previous week, but I attributed it to the stress of caring for my brother-in-law's

family. Little did I know, this was just the beginning of a harrowing battle for my life and quality of life, one I could never have imagined. On November 13, 2020, I went to the local hospital ER, where I received the confirmation of a positive PCR test for COVID-19. The bloodwork revealed somewhat concerning results: a low white blood cell count at 3.8, diminished lymphocytes at .7, and borderline low platelets at 153. I felt both relieved and anxious, knowing I was sick but unsure of what lay ahead. They discharged me with little guidance.

Just two days later, the situation escalated. Back in the ER on November 15, I was overwhelmed by severe pain coursing through my body. It felt as if someone dumped a bottle of Icy Hot or Bengay all over the inside of my whole body. My chest pain intensified. Lightheaded and on the verge of collapse, I desperately clung to the hope that medical staff could offer relief. My bloodwork had worsened: a WBC of 2.1, low lymphocytes at .8, and troubling signs from imaging studies showing many Ground Glass Opacities from the CT scan. Despite my pleas for Remdesivir, I was told I didn't meet the criteria for hospitalization, I was too young, had no pre-existing conditions, they were short staffed. Again, I was discharged, but this time, I started to feel a sense of dread. My husband became very ill with COVID-19, leaving me to care for our two sick children. My son exhibited neurological symptoms—delirium, excessive drooling, and terrible confusion—while my daughter struggled with severe fatigue, making it difficult for her to walk or even get up to eat or use the restroom. Since that infection, she has faced ongoing fatigue, stomach pain, eye problems, insomnia, and unusual bruising and abnormal platelet tests. Both of my children have had more frequent infections since COVID, about 2 infections per month, sometimes more. During this time, we were in survival mode, navigating each day with hope that symptoms would subside. By the end of November, some signs of recovery emerged. Though I still battled relentless headaches, body pain, and chest discomfort, I clung to the belief that I was turning a corner.

To further investigate my low white blood cell counts from the COVID-19 infection, my doctor referred me to a hematologist. On November 30, 2020, during my first visit, my WBC was still low at 3.1, with Neutrophils at 1.7,

But my Lymphocytes and Monocytes had returned to normal levels. My Plasma Cell Profile and other hematology tests appeared normal, yet I couldn't shake the feeling of uncertainty that lingered.

It seemed like things were finally improving. I felt well enough to take my kids for a walk along a short stretch of Lake Michigan shore and visit with a friend. But on December 10, 2020, everything changed. I woke around 2 a.m., drenched in sweat and grappling with a wave of nausea that felt insurmountable. My chest pain shot to a 9 out of 10, and my heart raced uncontrollably. I rushed to the bathroom, where I vomited so forcefully that it came out my nose.

Despite having visited the ER multiple times without relief, I knew I needed help, so I went to Urgent Care. Bloodwork revealed a WBC of 4.8, low lymphocytes at 0.5, low monocytes at 0.2, and neutrophils at 4.1. My platelets were back up to 214, but the D-Dimer showed a positive

result at 0.52—previously negative. The ECG reflected abnormalities similar to those in October 2020. Yet again, no one could offer a solution or information.

I tried to reassure myself that things would improve. But by December 12, just two days later, I found myself back in the hospital ER. The chest pain had intensified, accompanied by tachycardia and relentless palpitations. My insomnia reached unbearable levels, each night feeling like a battle for breath, as if I were drowning. The moment I felt the wave of sleep coming on, my body would jerk awake, leaving me wide awake and trapped in a cycle of exhaustion and fear.

My WBC count was notably different this time when I arrived at the ER on December 12, 2020; it was at 10.1. This increase was all in Neutrophils, which were alarmingly high for me at 9.3, while my Lymphocytes plummeted to a concerning 0.4. It felt ominous to have such elevated Neutrophils in just two days alongside such low Lymphocytes, especially given my troubling symptoms. My D-dimer had risen to 0.63, higher than just two days earlier, and my Lipase was low at 62. A Respiratory Pathogen Panel was run, returning negative for all 20 viruses tested. A week later, I was scheduled for an Echocardiogram. It revealed an elevated Right Atrial Pressure (RAP) at 8 mmHg and a lower than expected Ejection Fraction (EF) of 58%.

The relentless night sweats continued to plague me. I began to notice involuntary tics or twitches whenever I was at rest. When I closed my eyes, it felt like a lightning storm was happening behind my eyelids, with bright flashes of light that disturbed any semblance of peace. The nausea was overwhelming—like pregnancy morning sickness but magnified fifty times. Swallowing and eating became a daunting task; it felt like a lump lodged in my throat, making it painful to swallow. Numbness and tingling cascade through my hands and feet, which were always cold and discolored now. The severe headache that had seemed to wane at the end of November reemerged with a vengeance. It was a terrible burning pain on my whole head that refused to relent, a constant reminder of my suffering. I experienced pressure and fullness in my ears, and after bouts of explosive diarrhea on December 10, I was met with months of painfully severe constipation, sometimes going weeks without relief.

The month of December had descended into a nightmare. The insomnia was unimaginable. As someone who had always over sleep and was known for being a great sleeper, I now found myself barely managing 1-2 hours a night. For a couple weeks, it was even less. I could feel my body shutting down. Napping during the day was futile, no matter how hard I tried.

I struggled to smile at my kids, to laugh at jokes—my energy for even basic movements around the house had vanished. I was trapped in a cycle of sleeplessness and pain, unable to rest or find relief. My memory faltered; I couldn’t recall a conversation with my spouse ten hours later. Driving became impossible, and even watching TV or reading a book was too difficult. My family was frightened, and I prayed every moment to survive whatever this was, hoping to hold on until my 40th birthday in January.

Miraculously, I made it through Christmas. Just being with my family and mustering the energy to put a smile on my face for my children. But all my symptoms persisted and worsened,

leading to another visit to the ER on December 27. It wasn't the merry Christmas I envisioned but I was alive—and for that, I felt grateful.

This time, at the hospital, my D-dimer was elevated but had decreased slightly to 0.59. I still faced another CT scan to check for a pulmonary embolism (PE). While many Ground-Glass Opacities remained in my lungs, thankfully, no PE was found. My WBC count stood at 6.7, with low lymphocytes at 0.9, normal neutrophils at 5.3, and platelets at 202. My venous blood gas results were abnormal, showing low PCO2 at 36 and low PO2 at 33, yet again, there were no clear answers. I was discharged without any real help New Year's Day is not a time you want to find yourself in a hospital. Most people envision sleeping in, enjoying meals with family, or making plans for the year ahead. But that New Year's Day, a severe snowstorm hit where we lived, making an already daunting task even more challenging. After weeks of little to no sleep and a body that felt like it was unraveling, no answers or help, I had to try seeking help again.

We attempted to drive to a different hospital, hoping for better care. However, as the snowstorm intensified into a blizzard, we reluctantly returned to the closest hospital.

They performed a COVID-19 PCR test to check if I still had the virus; it came back negative. My white blood cell count was normal at 5.3, but my lymphocytes were low at 1.0, and neutrophils were at 3.6. All other tests, including troponin, CRP, INR/PT, PTT, and BMP, returned normal results, just as they had before. An endocrinologist noted elevated epinephrine in my 24-hour urine test, at 17. The ECG remained abnormal, showing inverted T waves, along with indications of right atrial enlargement and prolonged QT interval. Yet again, the ER doctor was at a loss for how to help me. However, she referred me to a cardiologist, the first of three I would see.

Around this time, the severe nausea, the lump in my throat, extreme difficulty swallowing, constipation, and lack of appetite became noticeably worse. I could barely get down liquids. I would blend cooked chicken, kale, apple juice, and broth, trying to consume as much as I could around 1 PM—the only time my nausea would subside a little. I took Zofran almost every day to help keep things down. Despite my efforts with protein shakes and blended meals, I undesirably lost 15 pounds in just two weeks.

Describing the struggle to swallow is difficult; it took all my energy to manage even one gulp at a time. It felt as if my entire GI system had just stopped working. I could barely swallow or have a bowel movement for weeks. On January 8th, I saw a Gastroenterologist PA. An abdominal X-ray revealed moderate amounts of retained stool in the ascending and proximal descending colon. They recommended a colonoscopy and EGD, but I could barely walk. A friend had to drive me to the appointment and wheelchair me in. I was sleeping only 2-4 hours a night and could barely talk due to my low energy. My headache remained severe. Despite everything, I made it to my 40th birthday. Friends sent gifts and wrote messages, reminding me that even while I felt like I was falling off the face of the earth, people still cared. Although I continued to experience many of the same debilitating symptoms, things seemed to hold steady, and they weren't getting worse. I could not work, care for my children, or fulfill my roles at home. We had to hire someone to help with meals and with picking up and dropping off the kids. I am incredibly grateful to my spouse, who was a pillar for our family during this time, and to my

parents for helping to cover the costs of hiring someone to care for my kids while I was unable to. Friends also pitched in, doing our grocery shopping, and bringing over meals. While symptoms persisted through January and February, I occasionally felt glimmers of hope. I continued to experience a range of debilitating symptoms, including terrible nausea; throat pain; a lump in the back of my throat; gastrointestinal distention pain and gurgling; constipation; a lack of appetite; difficulty swallowing; a dry cough; and chest pain. My heart raced with palpitations, and I battled low blood pressure, night sweats, involuntary muscle tics, and widespread numbness and tingling in my hands and feet. My extremities felt cold, and they were most often white or purple. The severe headache was relentless, night and day, accompanied by bright flashes of light whenever I closed my eyes or tried to rest. I could describe it as watching a lightning storm behind your eyelids. I struggled with insomnia, managing only 2 to 5 hours of sleep each night, and the sensation of drifting off to sleep often jolted me awake, leaving me unable to rest for hours. To cope, I had to sleep upright in a chair, wearing an ice helmet on my head and a heating pack on my stomach and hands. It felt as if my circadian rhythm was switched. Days blurred together as I navigated this overwhelming reality. On March 10th, I developed a new and alarming symptom: a red flat rash above my navel. It quickly spread to my whole abdomen, torso, breasts, and inner arms, transforming from an initial slightly raised bright redness to tight, painful, dry, and shiny skin. The fragility of my skin became evident as even minor movements felt like it might tear.

After visiting my doctor, further tests revealed some shifts in my lab results. My D-Dimer normalize at .42, but my Ferritin was low at 11. My white blood cell count was stable at 4.5, and all other markers appeared normal. However, the testing journey continued as I was referred for my first pulmonary function test, which showed abnormal results, including hyperinflation, gas trapping, and increased diffusing capacity.

In April 2021, I saw a Vascular Specialist who diagnosed me with Raynaud's Phenomenon, a condition that causes my blood vessels to constrict excessively in response to cold or stress, often resulting in numbness and color changes in my fingers and toes. I did not have this before. Alongside this diagnosis, I developed excruciating tooth pain and heightened sensitivity that made even gentle brushing unbearable.

The rash persisted, peeling and hardening the skin. It felt taut and uncomfortable, like a second skin that restricted my movements.

As I attempted to stand and move around more, I noticed a troubling increase in lightheadedness and dizziness. At times, I felt as if I might faint, and even while sitting in bed, the room would spin around me, making every simple task feel daunting. The fatigue I had just moving around my house was startling and debilitating.

As spring unfolded in April and May, I often found myself gazing out the window from my chair, appreciating the emerging flowers, the rustling trees, and the playful squirrels. Nature’s beauty was a bittersweet reminder of what I longed to experience again. My mobility remained limited, my skin dry and fragile, like newspaper. The symptoms I had endured since December and January lingered on, though they were slightly less severe.

Towards the end of May, I woke one morning with an alarming new symptom: right eye apraxia. My eyelid refused to open on its own. Once I managed to pry it open with my fingers, sharp pain shot through my vision, forcing me to shut my eyes immediately. Both eyes felt painfully sensitive to light first thing in the morning. Throughout the day, my vision was blurred and delayed, slow vision, each glance a reminder of my deteriorating health.

Concerned, I consulted a neurologist who admitted uncertainty, remarking that COVID was wreaking havoc on some individuals in unpredictable ways. He referred me to a neuro-ophthalmologist, who conducted a battery of specialized tests in search of answers. I appreciated his thoroughness, yet each test yielded no clarity about the sudden onset of apraxia and vision changes.

At the same time, I began seeing a new cardiologist. My 12-lead ECG again showed inverted T waves and signs of left ventricular hypertrophy. The doctor speculated about potential pericarditis or myocarditis. After careful consideration, we decided to try colchicine for three months, hoping it might alleviate some of my symptoms.

As June began, I found myself grappling with the distressing reality of having lost over 40% of my hair that month, alongside the persistent symptoms that had plagued me since December 2020. My primary care physician tested me for the SARS-CoV-2 Nucleocapsid Protein IgG, and to my shock, the result was negative. Despite this unexpected news, I decided to receive the COVID vaccine. Afterwards, I noticed an uptick in my chest pain, and my symptoms worsened.

In July, after receiving the second dose of the COVID vaccine, the chest pain intensified alarmingly. I visited Urgent Care, but they recommended I go to the ER—yet after my previous experiences there, I couldn't bring myself to return. I continued to manage the relentless chest pain, severely limiting my activities.

Nights were particularly challenging; I experienced burning pain in my big toes and head, and my legs would thrash uncontrollably. Frequently, night sweats would drench my sheets still. Fatigue had become a constant companion. Though I could still drive and prepare meals for my children, even the simplest tasks left me utterly exhausted. This fatigue was unlike anything I had ever experienced—so heavy that neither sleep nor rest could alleviate it.

Continuing to see more specialists I saw a Pulmonologist in July and a Dysautonomia Specialist. Of interest, my Blood Gas, Arterial was abnormal. PH was high 7.52, PC02 Arterial was low 27, P02 Arterial was low 61, HC03 Arterial low at 22, 02 Saturation Arterial low 94, Oxyhemoglobin Arterial low 92.4, and FI02 was 15%. The Arterial blood gas was repeated with similar results. I also found out I am a heterozygous carrier for AIA deficiency. My AIA levels were in the normal range though. The Dysautonomia Specialist completed a tilt table test, sweat test, and breathing test as well as bloodwork. Diagnosis: mild POTS. Not enough to explain the low blood pressure, dizziness, GI issues, lightheadedness, or all of the related symptoms. By mid-August, I had completed three months of Colchicine, taken twice daily, as prescribed by a new cardiologist (the third one) I had seen in the spring. To my relief, my sleep significantly improved this month; I started getting 5-7 hours of uninterrupted rest. I began to wonder if my

previous sleep problems were linked to heart and cardiovascular inflammation? Despite this progress, I still wore an ice helmet to bed to manage the severe headaches and had to sleep elevated still due to difficulty breathing when lying flat. The night sweats had decreased, and I finally felt as though I was coming back to life. However, I now had to take Zyrtec daily to combat the extreme itching sensation that would leave my skin feeling like it was on fire. At the end of August, my primary care physician and I decided to test my SARS-CoV-2 Spike Protein IgG. Having contracted COVID-19 twice in the past year and received two vaccine doses, I expected a robust antibody response. However, my result was only 82.6. My hematologist later explained that a solid response would be above 500, leaving me feeling disheartened.

In October, I received my third dose of the COVID vaccine. Just 14 days later, I experienced alarming severe chest pain and worsening fatigue, symptoms that persisted for almost three months. My cardiologist suggested I hold off on further COVID-19 vaccines until we understand more about heart inflammation from COVID itself or the vaccine.

There are many more parts to my story, numerous tests completed, and details I have not included due to time and energy constraints. After a bone marrow biopsy in April

2022, it was discovered that I have hypocellular bone marrow, with only 20-30% cellularity and no identifiable cause. The results ruled out oncological causes and aplastic anemia, leading to a diagnosis of Clonal Cytopenia of Undetermined Significance (CCUS).

This raises several questions: Was COVID-19 responsible for damaging my bone marrow and immune system? Did I have a pre-existing unnamed condition that I was unaware of, which contributed to the severity of my COVID-19 experience?

Currently, I now struggle with chronic low white blood cell counts and chronic low T-cell counts (including CD4, CD8, CD3, and NK cells). As a result, I find myself falling ill frequently, often from common viruses that my children bring home. What would be a non-severe illness for most can incapacitate me for months.

The symptoms I face now include heavy fatigue, persistent headaches, brain fog, neurological issues, paresthesia on the front of my face, eyelid drooping, chronic tinnitus, dry eyes, vision changes, cold hands and feet, exercise intolerance and PEM, gastrointestinal issues, and difficulty gaining weight. Frequent and more severe illnesses are among my most debilitating challenges at this time.

At the NIH, CDC, and FDA, every decision—whether action or inaction—has the potential to significantly affect a patient's life or quality of life. Individuals with Long COVID often do not respond to the virus or vaccines in the same way as the general population.

Personally, I experienced a poor antibody response to both the virus and the vaccines I received. It seems COVID has compromised my bone marrow, leading to bone marrow failure from an unknown cause. Despite undergoing two post-COVID bone marrow biopsies—one at

the NIH in Bethesda—there is no identifiable oncogenic cause, nor is it aplastic anemia. My white blood cell counts dropped after COVID and have never recovered.

I want to live, yet I question why there isn't more support for people like me to avoid COVID-19 and other viruses, especially now that my immune system appears dysfunctional. Why haven't more long-acting monoclonal antibodies been made available to individuals with Long COVID to help prevent reinfection? I wear a mask everywhere, but my children (one who suffers from Long COVID as well) and spouse continue to bring illnesses home, and I cannot live in isolation.

None of my clinical doctors are willing to explore potential treatments or medications unless they receive guidance from the NIH. Where are the NIH recommendations for those of us who want to improve our health but cannot afford to wait years for slow-moving trials? The time for action and expanding possibilities is now.

Many of us have already tried nonpharmacological strategies—resting, pacing ourselves, mind-body practices, supplements, physical therapy, breathing exercises, masking, isolating, and avoiding being indoors with people outside of our family—to reduce our risk of illnesses.

Since my COVID-19 infection in 2020, I have consulted over 45 different medical professionals. I am willing to donate tissue samples, bone marrow biopsies, blood, and share my electronic health records to help advance understanding of this disease and explore possible treatment options.

Sarah Majer-Powell, Susan Endres, and Carolyn Vollmer
Thank you for inviting us to share our perspectives. We understand and greatly appreciate that you are trying to help. However, the RECOVER initiative has made some errors that we hope will be rectified going forward. Please forgive our frustrations.

RECOVER's top priority needs to be deciphering the root mechanisms behind our exertional intolerance, dysautonomia, and other primary symptoms. Until we understand the root mechanisms, any treatments are like putting Band-Aids on bullet holes.

Post-viral conditions are not new. People with experience in researching conditions such as ME/CFS should be taking the lead in Long COVID research.

The ENERGIZE trial is at best misguided and at worst harmful. By suggesting cardiopulmonary rehabilitation as a treatment for exercise intolerance, you are downplaying our very real physiological illness and implying that it's merely deconditioning. For those of us with post-exertional malaise, there's a mountain of research demonstrating that exertion worsens our symptoms and can permanently lower our baselines, while those without PEM are a minority less in need of help. Even though you later split the trial into two arms, the pacing side isn't offering anything new because most of us are already practicing it out of necessity. The pacing arm also requires two in-person appointments per week, demonstrating a fundamental misunderstanding of pacing as this is in itself beyond the pacing limits of many of us. We understand that exercise is very good for most people in most circumstances. But you need to

understand and accept the evidence that a unique characteristic of our condition is that even light exertion can exacerbate our condition and cause us increased suffering with nothing gained. Please put your resources and energy towards finding and addressing the root cause of our PEM so we can exercise, which we miss being able to do.

This trial is wasteful and dangerous. It takes resources away from legitimate trials. It endangers participants' health—if they haven't yet triggered a crash bad enough to realize they have PEM—and could permanently lower their baselines. But possibly most damaging, it invalidate our suffering, suggesting that PEM does not exist and that our disease is simple enough to cure with exercise.

We need broader access to IVIG trials. This is a treatment that shows promise and is something none of us have a chance to get through insurance. The fact that the exercise trial is available in Pittsburgh while the IVIG trial is not, is irresponsible. Monoclonal antibodies, which are tailored to the COVID-19 strain the individual most likely contracted, is another similar trial worth doing and making widely available.

EBV reactivation and antibodies in Long COVID should be further studied.

Microclotting and endothelial dysfunction should be further studied.

Autoimmunity in Long COVID should be further studied and effective testing for it needs to be developed.

Trials should be brought to patients' homes whenever feasible in order to lessen the strain on them. This way patients in the worst condition can participate in trials without exacerbating their symptoms by the strain of travel.

These next items are not strictly about the RECOVER trials, but they are important to us. We hope you, as leaders in the medical community and federal government, will be able to help us or pass along our thoughts to those who can.

There needs to be clear, authoritative communication with Social Security, so people disabled by Long COVID have a path to disability benefits. Social Security is currently trying to deny our condition and deny benefits. Some of us have been unable to work for years and are still waiting for the benefits to which we are legally entitled.

There is a severe shortage of doctors willing to work with Long COVID patients beyond ruling out other underlying conditions—even within so-called "Long COVID clinics." We need doctors who think outside the box and who actually care about those of us who have become severely disabled by this disease. Our experiences trying to get medical care have overall been terrible, with doctors dismissing our symptoms, saying "there's nothing to be done," or simply passing the buck to the next specialty. Give us doctors who are actually up for a challenge. Give us doctors who aren't afraid of conditions or approaches that weren't in their medical school textbooks. Neurology, immunology, and rheumatology all need to step up and take

responsibility for their part in our condition. These specialties need to be trained out of the tunnel vision they acquired in med school and learn to look at the multi-system disease that is debilitating us. The NIH and all doctors and medical professionals need to stand strong against mask bans. Studies show that Long COVID patients are likely to get worse with additional COVID infections. We cannot imagine what worse than this looks like, and we and our caretakers need to be able to protect ourselves. Please do everything you can to fight for everyone's right to mask.

Thank you for seeking feedback and taking our concerns into consideration. We know some of these issues are systemic and won't be easy to fix, but we have nowhere else to turn. We need people like you to advocate for us and remind the public and our government representatives that COVID isn't over and isn't "just another flu." One mild illness and anyone could become us, losing their independence, identities, and lives as they knew it—unless you can help us identify the mechanisms causing Long COVID and ways to treat or cure it. Please continue to solicit feedback from patients and caregivers to keep our priorities and needs top of mind.

Appendix D: Virtual Questions

Monday, September 23

- Many people who logged on early cannot see the presentation. Can someone tell them to quit and rejoin? Worked for me. -Joseph Landson
- Excited to be here. Can you improve the audio? It is pretty rough. Thanks! -Rivka Solomon
- Will our microphones be enabled so we can participate as partners virtually? It was my understanding that we would be so allowed. Thank you. Larry Kleinman, Rutgers - Lawrence Kleinman
- We're here dual audio right now, echo. -Marrah Lachowicz-Scroggins, NHLBI
- Can Zoom chat be enabled to allow viewers to discuss items being presented? -Scott Daniska
- Thank you to Rivka for letting us know the audio is garbled. That probably explains why the captions are gibberish as well. Appreciated. -PF Anderson
- There are many people trying to be let in = any suggestions for them? -Lisa Berdan
- My registration provided two different Zoom links. One of them was wrong. I tried both several times before one of them worked. The registrants waiting to be admitted are probably in the wrong link. The emails were very confusing. These are the two links I received. Zoom Meeting Link: https://fnih.zoom.us/j/84466626093?pwd=e3wAzdDdvWaPbT9aztI5VAsaJxiT8M.1 Zoom Meeting Link: https://nih.zoomgov.com/j/1610641032?pwd=7aaP7KOKQirvsiCIEwwXJWVj1rj8T0.1 -- PF Anderson
- Will we be able to get a slide download? Please forgive me if I missed this. -Eileen E
- Will recordings be made available for later viewing. I have other appointments and do not want to miss anything. -Cindy Bartholomew
- Could you please update the funding situation for wastewater monitoring? -Cheryl Lohman, MD
- I am a virtual panelist tomorrow and need to confirm how that will be handled on Zoom - who should I reach out to? -JD
- Is there a reason NICHD is not a top line partner. From here it seems they need to be. - Lawrence Kleinman
- I had the same issue. I tried for 20 minutes to get in using a link sent to me on August 17th. I had to get a link sent to me from someone else to get in. -John Bolecek
- re. Creation of Community Engagement Committee -- who is poc? -Allison R.
- My question was answered, please delete. -JD
- The activists in the room shouted “Long Covid AIDS, Long Covid Kids, Antivirals Now, Biomarkers Now, Blood Test Now, Viral Load Test Now’ which mirrors this LCAP letter sent by people with Long Covid to NIH https://actionnetwork.org/letters/tell-nih-use-science-not-symptoms-for-long-covid what is NIH’s response to this declaration of

demands shared by the activists? What clear solutions, if any, are being implemented to meet the demands? -Joshua Pribanic

- I am hearing that some people can't find the link to the meeting, even though they registered. Can you please re-send to all who registered the link to today's meeting? Also, I'm sorry to say but the audio is still not great. Thank you for all the work you are doing! I am sure it is very hard. -Rivka Solomon
- I have had long covid for over 4 years (unable to work, financially devastated). I'm in the RECOVER study. I am partially recovered finally through functional medicine. Many in the conventional medical community don't even know what long covid is. American medicine and government is woefully behind where they should be on this topic. too much talk minimal action. This discussion sounds to me like it was appropriate in 2021. -KJ
- How does this impact the current RECOVER structure? NCEG? -Marta Cerda
- Please clarify - are community representatives MEMBERS of the Executive Committee? We need to have representation not just input - there are NIAID models for this. -JD
- Will there be a metabolism working group? Laura-Isobel McCall
- What kind of public reporting will there be for the TLC Executive Committee? Will it be subject to the FACA? -Michael Sieverts
- Are there mechanisms in place to ensure that researchers in different working groups regularly meet to understand each other's ongoing studies and assess where synthesis may be possible? -Emma Barratt
- I realize that this presentation is not involving the psychological part, but I am hoping to go ahead and pose the question for the moderator, as a person that has been living with Long COVID for over two years, what can be done to help those of us that are experiencing such isolation and feeling unheard, even by the physicians? Support groups are needed for this, as much as Alcoholics Anonymous is needed for Alcoholism. Thank you. -Virginia Alden
- how can patients become involved. -Danielle Gillan
- My question above is for Joe Breen, thank you. -JD
- For Dr Breen: How will experts be selected for each working group? -William Hu, MD, PhD
- Will Recover be doing numerous small scale exploratory clinical trials to help understand pathobiology? -Cort Johnson
- Need to INSIST on brevity from audience. -Allison R.
- Please ask my specific question, the specifics are important. -JD
- Onsite participants can ask direct questions in the room - thus you should be reading out our questions as if we were onsite. -JD
- I hear tons of comments from NIH about "need for feedback and community involvement", yet we are 4+ years into the pandemic and I haven't heard any instance of patient involvement/engagement/listening.... When will this change and how will the community be allowed to provide input? -Scott Daniska
- How would an interested scientist working in Long COVID join one of the scientific working groups. -Andrew Schamess

- Possible to exit presentation mode so speaker frame is larger? Thank you. -Sachi Ushihara
- Taking the parallels with HIV/AIDs, is there any plans to develop a Ryan White-type patient support system for those with Long-COVID? -Ryan Weeks
- How much contact is there with other countries that are much more advanced in looking at this because they took Long Covid more seriously much earlier unlike the government bodies in this country? -Ron Pearson
- thanks! -Eileen E
- Speakers asking questions need to speak into the microphone so we can hear. -KJ
- Q: will the executive committee reach out to Francis Collins and Anthony Fauci regarding their experiences/guidance of doing this (if not already? would be reassuring to hear you did). -Jon Douglas
- It is very hard to hear the speakers in the audience. Is there a way to turn their microphones up? Thank you! -Barbara Taylor (she/hers)
- Can the moderator please repeat the questions from the floor? — because we can't hear them. -jacqui
- Oh no, I know I sound like a broken record, but we can't hear some of the audience's questions. Tech help available? -Rivka Solomon
- Could the presenter repeat the questions asked by the attendees as the audio is poor? -Penelope (Penny) Markham
- As a long-COVID patient, I believe I speak for many in my situation, I'd participate in any investigation that will move the needle forward. Thank you for convening this meeting! -W
- This is very encouraging and exciting. If we had funding for this in early 2024, why did it take 9 months to get to this great kick-off planning meeting? Better late than never but. -Russell
- It seems like there are plans to include the ME/CFS experience and perspective, will they also be eligible for clinical trials? -Elizabeth Unger - CDC
- In response to recent comment, we at Rutgers partnered with the AAP and AAFP's practice based research networks as a way to democratize recruitment. -Lawrence Kleinman
- Are these RECOVERY groups comprehensively created? meaning specialist from Neurology, Cardiovascular, Pulmonary, and patient advocate? -Katie Gasemy
- As we talk about community involvement, please be mindful of how difficult it is for patients and caregivers to participate. Currently Meagan Stone is late to the in person meeting because the driver of the NIH shuttle does not know how to operate the wheelchair ramp. -Amy Torres Best
- How can I join the online support group that Christine Maughan the Patient Representative spoke about? -Robin Jones
- How can I join the online support group that Christine Maughan the Patient Representative spoke about? -Robin Jones
- Showers have become my Everest. ~Christine Maughan, Patient Representative -Allison R.

- I believe that this needs to be addressed by the Patient Representative as she just described my life. I hope someone addresses this. I will stop now. Thank you so much. -Virginia Alden
- I realize that this presentation is not involving the psychological part, but I am hoping to go ahead and pose the question for the moderator, as a person that has been living with Long COVID for over two years, what can be done to help those of us that are experiencing such isolation and feeling unheard, even by the physicians? Support groups are needed for this, as much as Alcoholics Anonymous is needed for Alcoholism. Thank you. -Virginia Alden
- As a long-COVID patient all of this resonates so much. Thank you so much for including patient voices. -Wendy Shenk-Evans
- If Christine Maughan or other speakers would not mind sharing a contact for them, I'd appreciate being able to reach out post seminar. -Patrick
- great job!!! -Danielle Gillan
- Christine...Could you please provide your long covid's nonprofit organization's name? Thank you. -Zoltan Komar
- Diagnostics for LC is badly needed in the US (there seems to be more awareness in Europe (i.e. at least Germany) and furthermore, the awareness of PCPs in the US. PCPs are very unaware of how to even treat LC and area LC treatment centers are overflooded with demand and not responsive in a timely manner. -IBekirov
- Thank you -Robin Jones
- Angela you are a hero. -Danielle Gillan
- Can you share the link to the YouTube video please? -Yoko Morris -UNC
- Re. "We do understand the psychological component of this disease is critical. For now, the focus of RECOVER-TLC is meant to be on interventional therapeutics for the cause and symptoms.": I hasten to add there is extensive research on the neurobiology of psychological illness and related interventional therapeutics. There is also good evidence the gut produces and regulates neurotransmitters like serotonin, dopamine, norepinephrine, etc., all of which are implicated in psychological states, such as depression. This is important. Please do not dismiss the potential viral cause for psychological symptoms. -Allison R.
- Great JOB. -Danielle Gillan
- Deep gratitude for Christine, Angela and Liza for speaking for all of us patients. We know what the effort to be there in person costs you. -Peggy Jackson
- Accessibility is an issue. -Danielle Gillan
- Why after 4 years are we perpetually rehashing these patient accounts. You are, or should all be well aware of them by now. -Jeffrey Hamilton
- Thank you for representing us and for sharing your experience. It's been very painful. I'm grateful to you for raising awareness, especially the fact that some of us are so sick we're confined at home and/or using a wheelchair or other mobility device when we leave home. Many people not experiencing Long Covid aren't aware of this. When you acknowledge it, it helps the rest of us. -Reda Rountree

- Regarding the Lisa's CRPS diagnosis, what therapies (pharmacologic and non-pharm) have been tried and what was the outcome thus far? -Jennifer Minhas (she/her)
- I find it problematic that this gathering has not mandated mask wearing given 1) the known risk of long COVID 2) the inclusion of current long-COVID patients who cannot risk getting COVID again. -Wendy Shenk-Evans
- what is your advice for people are following in your footstep to be efficient and organized to create impact? -Danielle Gillan
- for relevant speakers: how do you get diagnosed with pre-lupus or undetermined connective tissue issues? -Patrick
- Thanks to Body Politic for already publishing the Long COVID Survivors guide which includes many insights from lived experience as well. Would recommend all Long COVID researchers/clinicians get it. -Sarah Jolley
- How can I get involved with putting the symptoms together? -Robin Jones
- Q: with three patients discussing their harrowing journeys, why is it that POTUS nor POTUS scientific advisor or other senior science/health leaders have yet to publicly make a statement on long covid? only the directors here, not even the HHS secretary who has to sign off on new offices for these efforts. these stories will continue to be unheard until our public leadership speaks up regularly and often. -Jon Douglas
- When I was working, I was involved in advocacy and policy work. I'm wondering how long COVID patients can identify opportunities to participate in advocacy? -Wendy Shenk-Evans
- I have been sick since October 2020. -Robin Jones
- So grateful for these three patients and their willingness to share their stories. I notice all three have suffered severe symptoms. Is there a place in the RECOVER - TLC initiative for those of us with mild or moderate symptoms? Do we have anything to add that might not be covered by folks with severe symptoms? -Janelle Backman
- Can someone on the panel talk about the impact of Long Covid on children and families and what we can do to support them? -Megan Carmilani
- Question for Liza - which specific symptoms did Low Dose Naltrexone help with, and how long before the drug start taking effect? -Robbie G
- Can the speakers comment on what the activists have demanded for Long Covid in the meeting today, i.e., “Long Covid AIDS, Long Covid Kids, Antivirals Now, Biomarkers Now, Blood Test Now, Viral Load Test Now”, as to whether they recognize AIDS-like changes happening in people with LC, are they communicating this, and whether they’re requesting NIH meet these demands such as requesting NIH provide a SARS-CoV-2 RNA viral load test? -Joshua Pribanic
- I want to reiterate Angela's point that I think there are many, many people who have no idea they are experiencing LC and then continue to unmask, exposing themselves and others to re-infection). -IBekirov
- Question: Can all speakers at this conference over the next 3 days please be aware that when you say the suffering has been going on for 4 years that that makes some of us who have been suffering for decades with ME/CFS and Dysautonomia continue to feel invisible? Thank you! -Rivka Solomon

- Thank you to the patient & advocates for sharing your stories! I became sick in April 2020, and I echo everything spoken on the life altering disease that is Long Covid. I never knew this world of chronic illness and now see a massive call to action!!! The ME/CFS community is defined as the ""millions missing "" missing out of life. Covid has brought light to this extremely underfunded, under researched, & under treated. Thank you, everyone here who is engaged in finding treatment for LC and many illnesses that follow. -Katie Gasemy
- What accommodations are being considered to help families participate in clinical trials? -Megan Carmilani
- I hope to be there. -Janelle Backman
- Can you share the Instagram that was mentioned? -Carole Coulter
- The education needs to be FIRST with internal medicine and family medicine doctors to recognize long covid. Many of those people don't know it exists and is real. Often they gaslight by diagnosing LC as anxiety. Doctors don't know what POTS is, they don't know the symptoms, don't believe in chronic fatigue, they recommend exercise (which is a bad recommendation), they don't recognize MCAS. They don't recognize the hormone disruption (cortisol, serotonin) and how that is one cause of insomnia. Likely suicides are way up because of the insomnia from diagnosed and undiagnosed long covid. The biggest issue is not the patient population recognizing they are sick, it is the medical community recognizing symptoms as long covid. -KJ
- Can people with Long Covid submit their written statements? -Julie Lam (she/her) MaskTogetherAmerica
- Will there be a recording of this so I can hear it again as my my mind doesn't work as fast as the presentations? -Robin Jones
- The chat is still disabled? Also, the ability to send questions anonymously can't be clicked. Thank you. -Katie
- There's a lot of talk of patient experiences, but will patient hypotheses will be considered - and if so, at what point of proceedings might that happen? Emma Barratt
- May I say, as a longtime writer: that definition is well-written. Excellent work considering the parameters. -Janelle Backman
- Thanks, could you also share the slides? -Robin Jones
- The pediatric and adolescent population is mentioned in the 2024 NASEM LC Definition but not completely inclusive. The underestimation of impact on pediatric and adolescents. Why? -Nandini B Raj
- Does LC definition distinguish between symptoms resulting for direct organ damage occurring during he covid illness and would be expected to be a long term problem- e.g. lung or heart or brain injuries. -dichter
- Pediatric and Adolescent display very similar symptoms. They may express their pain in various ways and different aspects. Thank you. -Nandini B Raj
- Hello, may I ask why "at least 3 months" was included? I have heard stories from patients who were lucky enough to only have symptoms for less than 3 months but they still faced debilitating symptoms and I believe it would be beneficial to be able to help these patients as well. -Heba Amer

- In the past week, there have been a number of press reports of significantly diminished funding for Long COVID research. How does this or will this impact on the RECOVER Project? -PF Anderson
- Given that millions of Americans have been suffering with ME/CFS and other chronic illnesses for decades without awareness or funding (and ME/CFS is shown to be the exact same disease as Long COVID), would you agree that we should move away from the "infection associated illness" terminology that is neglecting million of Americans who have been made chronically ill from non-infectious causes and also need awareness and funding, and additionally for Long COVID it unnecessarily limits the scope of research and convinces patients of underlying cause which has not yet been establish which may encourage continued unregulated personal trials of dangerous experimental antivirals? -Scott Daniska
- With medically vulnerable people there, about a medically vulnerable population specifically affected by Covid, why wouldn't masks be required at the conference? -Gillian
- The speaker is saying this definition is a patient-developed term, and yes they had patients involved in drafting it, however they do not have consensus for the definition from the Long Covid patient community. LCAP has issued a working definition that we believe the NASEM definition does not represent, and that it opens up opportunities for misdiagnosis and missed treatments due its lack of focus on biomedical evidence. For reference, this is a version of LCAP's working definition for LC "Long Covid is a multi-systemic disease that damages organs, neurological, gastrointestinal, and vascular systems, and causes AIDS-like immune changes, with research pointing to SARS-CoV-2 viral persistence as a leading root cause and measurable diagnostic." -Joshua Pribanic
- Will NASEM change their definition that clearly defines Long Covid within SARS-CoV-2 viral persistence and immune changes if biomarkers for Long Covid are validated that clearly identify these two markers? -Joshua Pribanic
- The Americans with Disabilities Act needs more knowledge regarding this disease. -Virginia Alden
- When you send us the recording and slides from this webinar, can you also please send us an agenda that included the names of the presenters/panelists, and the moderator, with their contact information? -jacqui
- Thank you so much for researching and advocating for Long Covid. Outside of a research lab, most Long Covid patients live in a grey area at doctors offices. We have health problems as debilitating as cancer and yet are not allowed to try different pharmacological treatments. Most of us have lost our quality of life and capabilities in life. -michelle
- While I could not be more hopeful and grateful that clinical trials are being run many of us cannot afford to wait for years for clinical trials results or do not live in areas where they are being run. -michelle
- While the NASEM definition is necessarily broad, we need to base clinical trials off subgroups not, that broad definition. We have people who have ME/CFS. MCAS, Migraine etc. Clinical trials need to be based on those subgroups. -john bolecek

- Long Covid has many faces and affects people differently. My WBC counts took a dive after my COVID 2020 infection and have never returned to normal levels. I am in bone marrow failure now per bone marrow biopsy but not from an oncological cause and not from aplastic anemia. I get sick from infectious disease all the time since Covid 2020 mainly from things my children bring home as I limit activities outside of the house and mask if I do go out. -michelle
- Where can those of us with Long Covid go for medical help? Our local doctors office often throw their arms up with little to no information or support. Why are extended courses of antivirals, monoclonal antibodies, and other medicines that could potentially be helpful not more freely available to people with Long Covid? When will these clinical trials translate to being able to walk into a non research clinic and get some medical help with this debilitating condition? -michelle
- I was a very active person and now am fatigued to the point where I can't do the activities I used to that help keep my 64 year old self in shape, for example hiking and pickleball. I'm concerned that not doing exercise will speed up my physical demise. So I want to do some exercise. But I'm worried that pushing myself will backfire. How do I know how hard to push myself to maintain muscular strength as I age, but also avoid overdoing it and making myself even worse? -iPhone (16)
- She is saying "it unites everyone around a single definition", yet I've only heard advocacy leaders promote this term, and hundreds of patients ask this "infection associated terminology"" not be used repeatedly, and continuously ignored by these advocacy groups trying to stiff arm their own personal beliefs" -Scott Daniska
- How will RECOVER and other federal agencies address the lack of awareness of Long COVID; address and combat media disinformation; public denial and convey consistent messaging and updated information towards appropriative protective behaviors (e.g. masking, clean air in schools and public places, etc.) for all of us (adults and children) alike. -IBekirov
- @ Michelle ,is the CD4 T cell dive the cause of your problems? -Ed
- What if anything is being done to coordinate care and insurance companies, both health and disability? Is the definition being presented being codified in a way that requires disability insurance carriers to accept it and use it in the determination of disability? -Jody
- Regarding biomarkers: I am seeing low cd4+/cd8+ ratio & high ferritin "on a rolling basis"...(with negative HIV)...Any thoughts? synthetic organic chemist here... -Zoltan Komar
- Will RECOVER-TLC be looking at studying and treating Long Covid from different variants? For example, the Delta variant was one of the most severe and symptom-heavy acute infections, and many people like me were fully vaccinated and still got Delta and resulting LC. Unlike many people's experience with Omicron, the acute infection was nothing mild. From my experience talking with other Long Haulers, I have more LC symptoms (sometimes innumerable) than those who were infected Omicron onward. Thank you. -Katie

- I got covid March 2020 at 33yo. Athletic, healthy, very successful in my career. Now 38, I'm on SSDI and rely heavily on my mom for care. I've tried very experimental meds. My life is on hold indefinitely and I cannot be a contributing member of society. I only plan on doing this until I'm 40. I would like to know during this conference the NEW meds that are going to be trialed, and how quickly. Not ivabradine, etc. that patients have taken for years now with limited to no success. NEW meds. -Gillian
- What criteria if any has Recover produced to specifically address the me/cfs-like subset of Long Covid? -cort johnson
- Will your clinical trials include mental health conditions as well as the physical conditions that span across the whole body. -Katie Gasemy
- As a researched that studies multisystem, chronic diseases like Long COVID, my lab utilizes a complex systems biology approach to develop better biomarker models, but there is a major block to bringing multiplex approaches to the clinic, which I think will be necessary for effectively diagnosing and treating complex diseases like Long COVID. Could the panel comment on this? -MC Ammons
- Thank you to Dr Jerry Krishna for your possibilities mindset and making sure no one with Long Covid is left behind. -michelle
- The 3-month requirement may be valid for research, but the treatment community must be informed that patients can't wait for treatment in the first 3 months. -Ruth Melnick
- Q: how far away are some of these novel diagnostics from being used appropriately in these clinical trial / lab settings? I read many papers and have seen some extremely impressive technology that can detect RNA at extreme sensitivities. Also what about PET scan technologies to be scaled out to more sites which can help show a "difference" of immune activation" -Jon Douglas
- How can we identify providers in our states? My long covid clinic in Orlando, Florida is closing. we are being referred back to primary care providers how do we educate or identify providers motivated to help. -Danielle Gillan
- Recover spent most of it's money on investigational studies of it large cohort. Everyone is talking about biomarkers yet Recover has invested little in uncovering them. How will Recover now help to uncover these needed biomarkers? -cort johnson
- One problem in trying to group patients is that our symptoms keep changing and organ damage crops up at different times. -Ruth Melnick
- It's massively disrespectful that panelists and participants at the conference are not masking for the sake of the medically vulnerable Long Covid patients *well enough* to attend in-person. -Gillian
- 100% -Danielle Gillan
- I would like to question the reasoning because I was in a coma due to covid that lasted for 3 months, and I had to wait a year before any help financially. -Etienne Carignan
- Definitely there is definitely bias in long covid diagnosis particularly in black communities. -YVONKA HALL
- Shouldn't there be a requirement for clinician education nationally now that we have a definition? -Marta Cerda

- I wrote a proposal about it because there is a lack of African American representation in long COVID centers. -YVONKA HALL
- I truly wish this kind of phenomenal acknowledgement of Long Covid among the SMEs, Government, Medical community, and persons living LC also happens in Canada. We are in desperate need for this. Thank you! -Nandini B Raj
- If African Americans are not in the long COVID clinic how can we have a valid definition when the experiences of many are being left out. I have symptoms that are not listed and I have met others with the same symptoms. -YVONKA HALL
- Do you are seeing other communities like latin america or mexican? https://journal.chestnet.org/article/S0012-3692(24)03079-4/fulltext -Luis Del Carpio-Orantes
- How many children are being misdiagnosed with other illnesses when they have long COVID? -YVONKA HALL
- When will Long Covid Clinics have real tests and treatments? Also when will they have real information based on current science? For example UC Davis is still treating based on references from 2021 and before that only is based on psychological effects. -Dara York
- Thank you to this lady for bringing up LC in pediatrics and adolescents. -Nandini B Raj
- @CaroleCoulter. I think it was #WeAreThe Wayside. -Melissa Charles
- There are a number of young children in urban communities that are not doing things that they would measure development milestones and I truly believe that they impacted by COVID. -YVONKA HALL
- I am sorry if this was addressed earlier - are the sessions recorded and will it be shared with the registrants? -Vidya Sundar (UNH)
- What if HHS required each health system to participate with this group and be required to report back to their teams to expand the communication and understanding throughout the country. As a note, I am a patient that had a mild case of covid in Dec 2020 (plus multiple reinfections) and have been suffering with LC since and yet my Dr. has given me little support and makes me feel unheard. -Marcia
- Not a question: Thank you for manning the online Q and A! Much appreciated, hope you have a wonderful day. -Emma Barratt
- Cut the mikes during breaks? They are potentially catching private conversations. -Lucy
- because of general issues of the pandemic which caused confusion, lack of resources and high turnover in the medical field, I have been assigned to 3 different PCP since 2022 I was told by one provider that I could send them research but they wouldn't read them and my current PCP just says they are not trained in understanding long covid & when I send them current research data that supports trying a different medication or protocol they won't try it because of their lack of knowledge I was told to find a clinic myself-very difficult with limited energy and cognitive impairment- as I feel up to it, I have been trying to find a clinic since a few months after my initial covid diagnosis in 2022 How can the medical community, especially PCP be encouraged to learn more about long covid given the systemic issues in the medical field-even if they wanted to learn a lot more, they have no time. -Linda Patton

- Hi, is it started, it only showed Lunch page on my zoom. -Tongcui Ma
- YOUR MICROPHONE IS MUTED ;) -Katie Gasemy
- Hi, the screen is black—is lunch over yet? -Amy Geng
- You are just describing the benefit of creating universalized terminology, there is nothing specifically beneficial about "infection-associated illness", which just marginalizes patients and limits research and understanding among a vast and diverse patient population with a diversity of initiating events. The reality is we can be MUCH more inclusive than using the term "infection associated illness", although advocacy leaders don't like to admit that. -Scott Daniska
- I understand why we need power in a study, but I do want to know what is the prevalence of sub groups of LC (i.e., neuro LC) and prevalence of those with overlapping subgroups. -Jennifer Minhas (she/her)
- Just want to note that the audio quality remains pretty awful. While I can understand the speakers, their voices are muted and I have to strain to listen. It would be great if this could be resolved in future sessions. -Ezra Spier
- Is there a way to only have the speaker on the side-by-side view? It's distracting seeing 2 others - one who keeps turning camera on and off and pops on and off the screen, thanks! -Katie
- We don't have time to do things in the deeply thorough, rule by rule way that would be preferred. People have lost their lives, families, jobs, homes. We need to do this in a more expeditious way. Please address this concern. -Gillian
- Is there a way to find/join a clinical trial? -Robin Jones
- Dr. Al-Aly, can you talk about prevention strategies for people who cannot take COVID vaccines due to the same reasons these people developed Long Covid due to autoimmunity, a.k.a. production of problematic antibodies that trigger inflammation of organs. -Julie Lam (she/her) MaskTogetherAmerica
- Just want to say my audio quality & volume have remained excellent & I greatly appreciate that this is offered online! -Cheryl
- I may have missed this, apologies if so, but will slides be shared with attendees following the meeting? -Julia Rozman (BARDA)
- Thank you, Dr. Al-Aly for talking Long Covid affecting all the organ systems! -Julie Lam (she/her) MaskTogetherAmerica
- Why is funding per patient so low when compared to other diseases. Does the panel feel funding is the biggest obstacle to making progress. -George Gomes
- Dr. Aly is phenomenal!! Thank you! What a phenomenal presentation. -Nandini B Raj
- Thanks!! -Robin Jones
- Does he know that 25-45% of ME/CFS patients never had an infectious initiating event (and this percentage may be significantly higher as non-infectious cases may choose to self-identify with other diagnoses like EDS and POTS), so why would he label it an "infection associated illness"? I developed ME/CFS from a chemical exposure in the workplace… am I supposed to write that the chemical gave me an "infection associated illness" on my incident form?? -Scott Daniska
- I missed the start of this section, which expert is speaking right now? -Sarah Boden

- Best presentation by far. Thank you Dr. Al-Aly!!! -jeffrey hamilton
- Why are the causes of Long Covid continually over-complicated? While there are many different symptoms, almost ALL of these symptoms can be attributed to excess inflammation (that can also lead to autoimmune responses). Certainly there are subsets of patient's that way be responding differently to inflammation. The question then is what is causing inflammation. Increasing evidence suggests that Most of the inflammation is due to sequestered viral replication and altered immune function. -jnovack
- Thank you Dr. Al-Aly. Your recent review and capturing what people suffering LC are experiencing are spot on. -IBekirov
- Great presentation Dr. Al-Aly. The comment on chronicity is so important. There's definitely a difference between a patient with symptoms for 3-6 months who MAY recover on their own or with minimal intervention and a patient who has been sick for 3-4 years already and will likely NOT recover on their own without significant intervention. -Michelle Winer
- what is urgency not being addressed? I would rather see quick research done based on what we already know. It's obvious that we need a good case definition for research but we needs results and to see which group can provide this. -Annette
- I really appreciate Dr Al-Aly's ongoing engagement as a physician scientist with the general community. HHS needs to ensure funding for the Long COVID Office to ensure high quality and national engagement with the public both digitally and on-site, among both the medical and non-medical community. How do we ensure HHS ensures funding for this type of engagement? Thank you. -Andrew Wang
- I loved to see Dr. Al-Aly leading by example by masking :) -Julie Sullivan
- Thanks for advocating for safe spaces. The resistance to using masks and/or providing telehealth when caring for folks with long COVID is absurd. It is ableism. -Cindy
- Not a question, but a thought your slide show moving around is like the disease. It changes constantly and you never know what you're going to wake up to. -Becky Moore
- Thank you Dr. Ziyad Al-Aly for your presentation! I appreciate your passion and candor, and your acknowledgement that LC patients had it right from day one and how important it is to listen to and believe patients! -Karen Kennedy
- @Robin Jones: if you also have ME/CFS too you may be able to join a clinical trial at Brigham and Women's Hospital, run by David Systrom MD: https://www.omf.ngo/the-life-improvement-trial/ -Rivka Solomon
- Can you put a link to the definition in here? -Christie Welsh
- Why did NIH not request more money for RECOVER from Congress for the FY25 budget (or the FY24 or FY23 for that matter)? How can this important work we are discussing today happen without annual money from Congress? -john bolecek
- Again, lack of abnormal lab results on standard blood testing means that a much more sophisticated diagnostic testing panels need to be done that correspond to the different sub-types of LC. (e.g. assaying mitochondrial function, microbiome analysis, oxidative stress, etc....) -IBekirov

- What issues are being faced due to a lack of new WHO variant names? As discussed, it seems different variants may impact patients differently, would it be worth separating the omicron era further? -Hannah Nicoll
- are long covid and long vax similar or different disease processes? -Danielle Gillan
- thank you! -Sarah Boden
- The commenter Cindy should be made aware that plenty of panelists and participants at the conference are not masking. Ableism even at a Long Covid conference. Gillian
- There is indeed symptom heterogeneity - but also some very clear and very common extremely debilitating symptoms (namely Fatigue, PEM, OI) - i.e. I believe we have a good sense of what is causing the most suffering and economic impact. There is clearly a balance between continued observational research and understanding the disease and attempting to treat it (clinical trials). However, it seems clear that clinical trials CANNOT wait for a full understanding of the disease - we already do know so much about it, and have relatively easy to measure outcomes on key debilitating symptoms. "We don't know enough to do a lot of clinical trials" feels like an excuse in many ways. There is some risk that we have subgroups that we have yet to identify which may hurt the clinical trial performance, but that can all be discussed transparently. -Chris Nowak
- It's very hard to hear. Subtitles if possible might help. -Gillian
- The sound is garbled. -Lucinda Bateman, MD
- audio not clear for Dr. Koralnik. -Lena Al-Harthi (Rush Medical College)
- I got covid March 2020 at 33yo. Athletic, healthy, very successful in my career. Now 38, I'm on SSDI and rely heavily on my mom for care. Ive tried it all including very experimental meds. My life is on hold indefinitely and I'm in physical pain. I only plan on doing this until I'm 40. I would like to know during this conference the NEW meds that are going to be trialed, and how quickly. Not ivrabadine, etc. that patients have taken for years now with limited to no success. NEW meds. ASAP. -Gillian
- The current speaker's audio is cutting in and out, FYI. -Ezra Spier
- The sound is not very clear. FYI. -Amy Engebretson
- Since it can be challenging for the conference staff and facilitators to record all of the feedback from the public on NIH's work on Long COVID via this digital platform, is there other mechanisms for attendees especially from the public to provide comments/feedback? Thank you. -Andrew Wang
- Dr Ziyad Al-Alys you are a champion for people with Long Covid. Thank you for all your and your team's dedication and work. Your passion to advocate and help patients, your Rule #1, it will change lives for the better. -michelle
- Yes, please remind speakers to talk close to the mic. It is difficult to hear them online. -MC Ammons
- is there a better way to get connected to research and clinic trials. I am a March 2020 long covid patient still with symptoms. I have been part of two research groups at NIH since 2020 and been to NIH for testing 4 times. However I seem to not be able to find and apply for newer research or clinical trials. Some of the search engines are not very user friendly for sorting.. THANKS for all you do. -Kelly Keeney

- A lot of this boils down o data collection at the doctors appt. being correlated across many practices. The Va of salt lake took a unique approach to this by having multiple doctors from various felids on one team taking care of the covid patients in conjunction with the primary care . why cant this be done across all hospitals and clinics . US wide and have data centralization. -Etienne Carignan
- Is there a component to RECOVER-TLC that has to do with mass public awareness efforts? As the speaker noted, there are many potentially with LC who are not being identified and therefore are not being studied. Perhaps this will be addressed in another session? -Peggy Jackson
- Just want to share that I got Long Covid even though I had received two boosters, one about 2 weeks prior to my infection. It's important to look at more than vaccines when it comes to Long Covid prevention. -Ezra Spier
- Question for the panelists re: trial designs: Will pre-pandemic ME/CFS patients be allowed to join RECOVER clinical trials? -Rivka Solomon
- @karen bishof, yes, that is how I have been searching, it is quite difficult (especially for a l.c. patient to sort through all the results AND if we don't search the properly we can very easily miss the one that we might fit into. -Kelly Keeney
- Pollett sounded great. -destry
- Question for Dr. Al-Aly: Of the 400 million you report as having had long COVID by the end of 2023, what percent do you estimate to have largely recovered by today, even if some symptoms do persist? By largely recovered, I mean someone who would be well enough to work full-time if they desired to do so. -Maureen Hanson
- What education is being provided to doctors on long COVID so they no longer deny it's real? -Sara
- Can you agree that HIV/AIDS pathologies are also not a monolith, yet they are all outcomes tied to viral persistence? -Joshua Pribanic
- TO: Dr. Stockwell. What do you think ought to be the process for distinguishing inclusion of children and adolescents in some all age studies from pediatric or adolescent specific studies? -Lawrence Kleinman
- Was the neurosurgeon testing at Northwestern? What type of testing is done to evaluate Long Covid symptoms? -Melissa Charles
- That's Stockwell not Stockman. -Lawrence Kleinman
- In the US, what is being or can be done to encourage insurance companies to cover more comprehensive testing for long COVID patients to understand the underlying mechanisms for any individual patient, as well as covering emerging treatments such as anti-virals, IVIG etc. prior to various studies concluding? -Wendy Shenk-Evans
- EBV has been shown in the serum of covid patients. Disappearance was a good sign whereas continued expression after recovery was a good predictor of Long Covid weeks and months later. It that data confirmed and still useful. -dichter
- HOW TO dissect out the role of long-term carriage, methods for long term carriage, and how to separate out phenotypes of those of Long Covid versus Long Carriage with and without symptoms. -JOE JOHN

- What specific steps are being taken to ensure that children are appropriately included and represented in clinical trials? -Megan Carmilani
- It seems that prevention of symptom worsening needs to be addressed. Primary care education is so important. I would like to see every primary care office have an educational brochure, or sticker, or online message that says: "WARNING – If you have PEM, exercise with caution!" -Ann
- Are QEEGs acceptable tools to look at brain waves and function? -Melissa Charles
- Q: Will these clinical trials consider the new FDA guidance of emphasizing decentralized trials & point of care where they make sense if specialized equipment is not required (i.e. imaging, etc). -Jon Douglas
- Not every state even has a RECOVER site. Can a RECOVER site be added to the missing states? -Gillian
- The meeting email lists phone numbers—you can call in and use that for audio (it is much better) and keep the video up at the same time. -Amy Geng
- I'm in NC now and the closest site is 6 hours away in WV. -Gillian
- Unsure who to address this to (Dr. Bertagnolli?) what is the NIH's plan for grant-giving for RECOVER-TLC? Is money going to be given to the same sites that failed to help us the first time? The old-boy's network of NIH's favored grantees? Or is money going to be given to the researchers who have advanced the understanding of LC and other IACCC's? -Amy Engebretson
- Are there clinical trials w/ IGIV or fecal matter transfer? -Laurie
- What can be done for a chronic cough which I developed after Covid. I also have asthma now which I never had before. My broncoscopy which was negative for everything except it showed a lot of airway inflammation. -Diana Letus
- I understand the 3-month defined time for determining LC but will there be a determination for when LC will lead to a flood of autoimmune diseases. The reason for Q is that many LC patients' diagnoses lead to ME/CFS / Dysautonomia / neuropathy, which have no treatment nor known cure, and only medicate symptoms. This creates a very different series of questions & direction. Part 2: If yes, LC leads to autoimmune diseases; will the time frame for LC leading the body open to autoimmune diseases determined to stop it before the flood gates open. -Katie Gasemy
- Maybe we can turn off the option for participants to have their camera on for now? -Christie Welsh
- Why have the RECOVER observational trials not focused more on autonomic testing, MCAS, and 2 day CPETs, all findings from ME/CFS that would be very valuable to replicate in Long COVID? -john bolecek
- How can lessons learned from current phenotype studies be applied to designing trials that are inclusive of early (wild type variant) patients? Considering that conditions have developed in early LC that are no longer evident in bloodwork. Can trials be developed based on symptoms alone? -Jennifer Minhas (she/her)
- Dr. Aly-Aly's 10% recovery rate underscores the urgency of this epidemic, especially with repeat infections increasing LC cases. Gillian

- In light of this response, do you agree that it's possible that Long Covid pathologies can also be showcasing outcomes that are tied to SARS-CoV-2 viral persistence? (these two questions are for everyone on the panel) -Joshua Pribanic
- are some types of long covid, such as POTs longer lasting? Lori Couture
- Do you expect everyone to have LONG COVID at one point in time who had covid once? What proof do you have that not everyone will have LONG COVID in 3-5 years down the line? -Zoltan Komar
- How are Long Covid researchers trained on ME/CFS prior to starting their trials? Cynthia Johnson
- I would like to speak to one of the Long Covid Investigators. Is this possible? -Alex Gressley
- Question to NIH Director and NINDS, NIAID directors: Knowing that Covid leads to Long Covid which presents as ME CFS type of symptoms with exertion intolerance in part of Long Covid patients, why hasn't NIH increased funding for ME CFS research in the recent years? -Madina M
- Is anyone on this panel testing their patients or participants in studies for SARS-CoV-2 viral load using a transcriptomic RNA blood test? -Joshua Pribanic
- I really want to have him follow up on the VA cube Dr.S imon Pollett -Etienne Carignan
- I believe it has been fixed. Thank you. -Allison R.
- Don't self-directed therapies, lifestyle choices, and epidemiological among other factors impact the information gathered during a clinical trial? -Isabel Silvestre
- I hope action items will be declared at the end of this conference to hold the NIH accountable for acting quickly. We're living in physical agony everyday. -Gillian
- Is RECOVER considering having a system where when someone suspects or has been diagnosed with Long Covid, that they can go to one of the existing (or future) RECOVER sites and "enroll"? Questionnaires, possible bio samples, any diagnoses the patient already has, and immediate treatment from the site that the patient can use right away. I tried to enroll in my RECOVER site for the longitudinal study in early 2022 (or maybe late 2021 can't remember) but it was already "FULL" which is inherently flawed. I understand limits on ability and resources but being told by our government quite early on that my site was full is demoralizing, creates deterrence, limits the population diversity, etc. Please consider having a way for EVERY patient to make contact with their closest RECOVER site going forward. Would also be a pool to pull from for treatment trials in future. Thanks. -Katie
- I know it is not the priority of NIH, but what can be done to educate medical providers about Long COVID? -Lucinda Bateman, MD
- How is Recover currently using its bio repository specimens to inform its search for biomarkers? -cort johnson
- what would be the reaction if a small pilot trial, let's say with 20 individuals with severe fatigue that interfered with may every day activities were suddenly able to get out of bed and function well with an entirely benign treatment? -dichter
- Thank you, Dr. Alba Azola :) Extremely important question!" -Katie Gasemy

- Further to Dr Hanson's question answered by live: I found it difficult to hear the precise % recovery rate that Dr Al-Aly mentioned. Audio quality issue. Thank you for providing that number in the chat. -Russell
- Questionnaires are not as important are actual dysautonomia tests, tilt tables, QSART, Skin biopsy for SFN, Valsalva Maneuver, MCAS tests, Serum tryptase, Chromigain A and of course 2 day CPETs. -john bolecek
- Is it possible to turn off the microphones during break? There may be side conversations that are unintentionally being caught. -Beth
- It's encouraging to see some panelists wearing masks. Could you help me understand why the NIH is not requiring all attendees and panelists to do the same? There is a current surge in Covid and the vaccination does not guarantee protection against LongCovid. You'd think the NIH panelist would understand Covid prevention. -Shannan Riemer
- My primary symptoms are brain fog and diffuse muscle wasting. I don't have the autonomic symptoms. Have you seen any other patients with muscle wasting NOT associated with inactivity? I have continued to exercise and do resistance training but have continued to lose muscle volume, to the point that I've had to discontinue my usual activities. I am a 50-year-old previously healthy female. Thanks. -tatum
- Do you have anything that helps for chronic cough? It started after I had Covid in 2020 and has continued. I have developed cough induced asthma a few years ago. I recently had a broncoscopy which all the test from it were negative except for increased neutrophils which showed a lot of airway inflammation. The doctor saw white milky mucus in my airways which I sometimes cough up but it is difficult to get up. I am on Trelegy inhaler & Ventolin inhaler. I use the nebulizer. -Diana Letus
- I missed the opening remarks and beginning of the workshop. How will I be able to access the recording? Thank you! -Cynthia Johnson
- I had to disconnect for a doctors appt. Will this webinar be archived anywhere so people can view sessions missed or for future viewing? Also, for those of us with cognitive issues it would be good to view again. Are there any contacts for long covid in New Jersey? Thank you. -Irene
- I also don't get PEM. I've had a full workup for muscle atrophy including ALS and mitochondrial disease. All the testing was negative. -tatum
- please ask the AV people to turn off the cameras of people who don't realize they have them on and are not involved in the session. Maureen Hanson
- Can someone please provide the publication/citation Dr. Elzakker referenced at the beginning? His publication? -Allison R.
- The share screen is not working on Zoom. -Katie Gasemy
- I agree with John above regarding the increased importance of objective tests rather than subjective questionnaires. -Brian
- There needs to be a caption on discussions like this that these patients are still actually sick... its not just "neurological feeling of being sick". Not discounting Michael's results, but there's too much overwhelming evidence of systemic, real, physiological effects outside of neurological brain centers. -Scott Daniska

- Question for panel: How do we get point of care tests developed for use of these mechanistic tests for clinical trial enrichment? Seems a limiting factor for clinical trials is the lack of available real time assays. -Sarah Jolley
- Thank you Dr Pretorius. How do we get this info to our doctors and Recover trials? -Dara York
- Are there other infection-associated chronic conditions associated with microclots? are there studies evaluating this? -Clementine Adeyemi
- Does RECOVER plan to attempt to replicate the microclot findings we are hearing about? -john bolecek
- I don't completely understand the biology of fibrin-resistant clots… Don't all clots eventually break down via the body's natural processes? What are those products. -Dan Kelly
- As spike is implicated in the microclots, is it a reason for Long Covid patients to no longer get vaccinated as spike protein is the basis for all the vaccines? -jeffrey hamilton
- For Resia, is the spike protein you find is implicated from the early pre-Omicron variants specifically? Have later variant spike proteins been implicated in the microclots as well? -jeffrey hamilton
- Would like to hear from Resia if she intends on manufacturing a small molecule composed of the antigen binding domain of a spike protein antibody that could block the formation of microclots and prevent them, and if this research is applicable to other indications for which microclots are seen. -Scott Daniska
- Thank you, Dr. Pretorius! Excellent presentation. -Julie Lam (she/her) MaskTogetherAmerica
- Are microclots still an issue in patients with bleeding disorders such as Von Willebrands? -Cynthia Johnson
- Question to Resia Pretorius: is it known whether the S1 region alone, or the full spike, causes microclots? NETosis? -Florence Herschke
- How then to interpret the fact that spike/S1 levels are highly fluctuating over time even in a single long COVID patient? -Florence Herschke
- Is anyone on this panel testing their patients or participants in studies for SARS-CoV-2 viral load using a transcriptomic RNA blood test to determine the amount of antisense RNA in the blood? If not, why isn't this test, the most sensitive type of test for SARS-CoV-2 viral load capable of finding replicating viral parts, being used? Isn't it possible that if you're not using this test it can mean the percentages of "viral load" in your studies that is determined by only looking at antigens is missing a large percentage of those with viral persistence? -Joshua Pribanic
- Doesn't the possibility of viral persistence argue for more aggressive treatment with antiviral treatment? Also, are combination anti-viral clinical trials planned (HIV is a well known model of treatment with a cocktail of antivirals, so why isn't the same being aggressively pursued for COVID and Long COVID)? -IBekirov
- Is there a hypothesis of how microclotting leads to dysautonomia/peripheral nervous system dysfunction related symptoms? And based on the proposed pathological mechanism is there a proposed treatment target? -Lindsay McAlpine

- What a fantastic presentation! Thank you for being here today. Regarding viral persistence, can I ask: how might viral load during exposure affect likelihood for developing Long COVID? Could post-exposure mitigation methods such as nasal sprays and/or CPC mouthwashes reduce viral load, potentially lowering likelihood of developing Long COVID? -elle seibert | got long covid?
- Does N (nucleocapsid) can also cause microclots in your hands? FlorenceHerschke
- Re Stanford study: including Ritonavir in the control group could have confounded the study. -Amy Engebretson
- Why is Vital adult only? Biological rationale? -Lawrence Kleinman
- I've seen a paper that showed that viral capsid levels do not correlate with long covid severity. Additionally, other similar conditions (chronic lyme, chronic EBV, etc.) for decades have been experimenting with antivirals/antibiotics for decades, most without beneficial results. What is unique about Long COVID that researchers are thinking viral persistence is relevant now, when in the past it's never been shown to have any therapeutic benefits (in majority of patients). -Scott Daniska
- Have you found differences in viral antigen persistence in CSF vs serum? -dichter
- Dr. Peluso, how about Long Acting Monoclonal Antibodies? -michelle
- Thank God for Michael Peluso!!! Please, please focus on the viral persistence studies he suggests!!!! -jeffrey hamilton
- Adding firsthand experience on microclots, I underwent triple therapy under Dr. Vaughn for 6 months. Initial screening showed highest level (4), after 6 months, re-test showed level 2. Fatigue and PEM level only improved marginally. It suggests to me that there is an underlying cause. My question is, has been any studies related to microclots before/after acute infection or any other to correlate an underlying cause? -paulk
- References for the RECOVER biospecimens Dr. Utz refers to can be found at the Ancillary Studies page, where protocols are also linked. https://recovercovid.org/ancillary. -Marrah Lachowicz-Scroggins, NHLBI
- Question to Mike Peluso: how many long COVID patients have both viral persistence. -Florence Herschke
- Are the study controls, who are being presented today, COVID-19 vaccinated or not? -Isabel Silvestre
- Dr. Peluso: if viral persistence stands ground and I believe it does...Then, does "reinfection" have meaning? Instead, the virus in the reservoir alternates between active & nonactive modes just like HIV does...No? Could you please comment? Could you please reas in my question to Dr. Peluso as my previous questions havent been answered. Thank you. -Zoltan Komar
- How are the rates of participation in Tier 2 and Tier 3 of RECOVER comparing to predicted rates, and does that inform consideration of these kinds of test in future studies? I have not been able to make most of my Tier 2 and Tier 3 visits, even with mild/moderate Long COVID as the scheduling is so tricky and it’s so far away plus people in the hospital outside the study area are unmasked. -JD
- Question to Mike Peluso: how many long COVID patients have both viral persistence and autoantibodies, or abnormal immune response to SC2? -Florence Herschke

- how early in the pandemic were samples collected? and from which body site? Are there other RNA viruses with similar biospecimen groups? and do you see this model being used for future viral outbreaks? -Jennifer Minhas (she/her)
- Is there a way for Long Covid patients who are not selected at a Recover Site to participate in Recover Trials if they qualify? -michelle
- Q: for peluso, you mentioned experimental trials, what about combination therapeutics such as mAbs, combination antivirals, etc.? -Jon Douglas
- Can the panel address the proposed mechanism for microclotting leading to dysautonomia (peripheral nervous system autonomic dysfunction)? Why aren't we seeing widespread clinical ischemic complications (strokes, MIs, PEs, DVTs) in long COVID? And what are the proposed treatment targets for microclotting? -Lindsay McAlpine
- Your recent Covid-19 infection was your first-ever time having Covid? -Reda Rountree
- Dr Utz, condolences on the loss of your godmother. Thank you for sharing your personal connection to this work. -JD
- PolyBio is the only institution I've heard of that is doing autopsy work... I wish other research institutions didn't shy away from doing that because we're seeing ME/CFS affect the tissue, not just the blood. -Scott Daniska
- Thank you PJ for your work! LC patient. -Marta Cerda
- This is amazing I am crying watching all the evidence and thoughtful approaches to help us… -Danielle Gillan
- Very true, Amy...Thank you...Thank you... -Zoltan Komar
- Such a huge thank you to all the researchers who are spending their careers working on this! -Amy Engebretson
- Dr. Breen, how is the work of this panel going to be integrated with that of the 2024 ME/CFS Research Roadmap? -Cynthia Johnson
- hello, my above comment was not addressed. did it come through on your end? -elle seibert | got long covid?
- Thank you for including the private sector (Michael Peluso, Amy Proal, Resia Pretorius) in the discussions. They have been instrumental in my maintaining hope. Without hope, this disease is unbearable! The only way to keep going is to envision becoming normal again! -jeffrey hamilton
- Just wanted to thank everyone's participation today & these next following two days. Really appreciate it. -Billy Hanlon
- Is RECOVER enrolling any long covid vaccine syndrome patients? (Those who are seronegative for antibodies to the nucleocapsid but have gone on to develop the same suite of symptoms as many long covid patients; clearly due to underlying MCAS)? As far as I can tell only Dr Iwasaki's team at Yale seems to have enrolled a cohort of long vax patients to study over time. Wouldn't it be worthwhile for NIH to study what is happening in these subsets of patients who are covid-naive but suffering nonetheless? -Ronak Kapadia

- Dr. Utz, you say “I got infected again 2 weeks ago, mild, fully recovered. Great opportunity for studies!” but I’m sure you realize you are not out of the woods for later emergence of symptoms - please continue to REST whenever you can. -JD
- There is a lot of accumulated research at this point. Shouldn't we move some focus to therapies which often result in valuable knowledge? -paulk
- Question for Amy - have we considered that the viruses aren't clearing due to hypometabolic immune cells? As we see evidence in low natural killer cell function etc. Since the question is WHY did these pathogens persist/not clear? -Corinne Dorfman
- Great, please do!! -JD
- To the trialists: how should we balance the burden on participants vs the need for comprehensive biosamples? -Ezra Spier
- Great talks! Good to "see" you, Resia and PJ! -Svetlana Blitshteyn
- Also: How important is it to enroll participants at different levels of severity? Severe and very severe patients are often unable to make any clinic visits, which would preclude biosample collection in many cases -Ezra Spier
- Please could you explain which tissues should not be included as biomarker for PASC clinical trials. -Getasew
- Dr. Utz, let me add my condolences for your loss. Such a very sad outcome for one who was clearly a wonderful woman. I have a question about your own experience with LC. You say you got COVID and went on to develop "new onset hypercholesterolemia, prediabetes, and hypertension" You also describe yourself as "fully recovered" (from your second acute infection). Have the chronic sequelae of infection #1 be "cured," or "controlled." Do you believe you still have LC? -Allison R.
- Who is looking at T cell profiling eg T cell exhaustion (males > females in ME per Nath ME phenotyping Feb)? -Megan McCoy
- Families often have more than one person with Long COVID or other IACC (like MECFS) or autoimmune diseases. Does RECOVER plan to study the role of genetics with LC? -Aimee Weiss
- How will you study the Long Covid patients who are most severely affected and are often bedbound? Aren’t most of the findings now skewed toward healthier Long Covid participants who can come to a study site? -Martha
- Thank you, Dr. Utz. I have Long Covid since my first and only infection from December 2020 and am also a Long Covid advocate. I’m enrolled in the Long Covid Clinic at UCLA with Dr. Nisha Viswanathan. I appreciate you speaking and sharing this information with all of us. -Reda Rountree
- Long Covid and RECOVER participant since March 21, Nuero. Are/can the biomarkers be ran for inherited mutations? -Meagan
- Thank you for being so forthcoming. -Allison R.
- Dr. Pretorius in a phenomenal scientist who has been talking about the micro-clots since before the pandemic. Many children living with Long Covid have shown to have micro-clots and clumping of platelets as biologic origins of Long Covid. Nandini B Raj
- Our new paper on Long Covid NOT being FND. https://www.mdpi.com/2075-4426/14/8/799" -Svetlana Blitshteyn

- Please include objective data in CT e.g. autonomic testing, skin biopsy, endothelial micro-vascular function, T-cell profiling, neuro-inflammation; subcohorts e.g., those with neurological impact (gastric dysmotility, cerebral regulatory function, neuropathy). -Megan McCoy
- Dr Utz, my condolences of your loss. Thank you for sharing something so personal with us. Thank you for saying many of you have changed your career focus to Long Covid. I've been very sick since 2020 and always blown away to hear some in the medical field that still haven't heard of LC; It's shocking at 4 plus yrs in. I am very grateful to nurses, physicians, clinicians, and researchers who have shifted focus to LC patients and finding treatment to this worldwide viral illness. Q: If there is evidence that covid spike proteins haven't left our body after years, does this mean the cellular makeup has been altered? If yes , is there research in development around this? -Katie Gasemy
- NFD cannot be proved or disproved as no objective data. Anyone can claim this at any time with no way to counter. Meant to be diagnosis of exclusion and in my experience as patient advocate and physician it is NOT THE CASE. Education needed. Neurologist. DOPAC for instance was found to be increased in ME patients… this can account for movement/ tremors/ body jerks. This is therefore not automatically “FND” due to stress of having disorder. -Megan McCoy
- Thank you, Ma'am... -Zoltan Komar
- This Ben luuft from Stony Brook. We have largely reproduced Michaels Study of microglial activation in PASC. However, we have further expanded these studies to examine diffusivity metrics indicative of axonal injury and neuroinflammation using MRI. These findings may offer another modality which may be useful in more widespread assessment of neuroinflammation. This could be an excellent biomarker as well as potentially a therapeutic endpoint -Benjamin Luft
- Is there evidence that repeat infections worsen long-COVID patients in the longitudinal RECOVER patients? -Frances Eun-Hyung Lee
- Dr. Pretorius - Are you aware of degenerative microdot deposits seen in corneal imaging associated with aging and could they be related to microclots? -Scott Daniska
- Lindsay McAlpine has very good paper on endothelial damage …. with subsequent decreased tissue oxygen update, micro-thrombi etc…German study showing pentoxyfilline working to help" -Megan McCoy
- is there motivation to set up more wastewater testing more globally, especially in countries in the global south, like Nigeria, that do not have effective testing currently to be able to better track variant growth? -Samarth Sandeep
- Is anyone looking into why Metformin seems to help some patients with acute Covid infection and help some patients with Long Covid? -michelle
- Failed paxlovid trial should teach researchers that we cannot put all our eggs in the "viral persistence basket", and need to consider other root pathologies. -Scott Daniska
- In the Paxlovid long-COVID clinical trial, did you happen to run the plasma for the highly specific spike and NP protein assays from M Peluso studies to see if there was some response in the 25% who may be positive? -Frances Eun-Hyung Lee

- What are he thoughts for why difficulty of B cells transitioning from igm to igg? -Dorothy Hassler
- Dr. Nath, you have recently advised clinical trial recommendations for Long COVID & ME/CFS that includes checkpoint inhibitors, JAK inhibitors, IL-1 blockers, IL-6 antagonists & TNF-alpha inhibitors & other immunomodulatory agents. You recommended that a platform trial (as seen in ALS) with these various clinical trial ideas could get to answers the fastest. Do you envision RECOVER being able to undertake this platform trial idea that you have stressed for? Billy Hanlon
- Please develop commercially available testing for T cell exhaustion (and look for additional treatments to check-point inhibitors). -Megan McCoy
- Dr. Nath, What is IVIG SUPPOSED to accomplish? Change the IgM>IgG block?? -JOE JOHN
- To Dr. Nath: did you test patients or participants in Long Covid studies for SARS-CoV-2 viral load using the transcriptomic RNA blood test to determine the amount of antisense RNA in the blood, to determine levels of viral persistence? If you're not using this test, and instead relying on antigen testing alone, isn't it true that you will not find the percentages of "viral load" regarding SARS2 viral persistence and therefore cannot make the statement that you believe Long Covid is from antigenic persistence and not viral persistence? And can you commit to begin using the transcriptomic RNA blood test in all your new sampling as well as those previously tested? -Joshua Pribanic
- Dr. Nath - could the reduction in norepinephrine in the brain lead to downregulation of IgM transforming to IgG? -Jennifer
- Dr. Nath, what pharmaceutical companies have you approached for partnerships, and around what drugs? You mentioned Bristol Myers Squibb if I heard correctly. -Rowan Walrath
- I am a (now disabled) ME/CFS patient who is (was) a professional fundraiser/nonprofit consultant. I am available to help obtain funds for the checkpoint inhibitor trial. I also have another immunologist/practice interested in a check-point inhibitor trial that I am working with. cadorfman@gmail.com. -Corinne Dorfman
- For the panel or anyone who knows:
- are there any plans to study plasmapheresis as a treatment or therapy for PASC? Patrick
- In May, a pre-print article, "Oxidative stress is a Shared Characteristic of ME/CFS and Long COVID" came out of Stanford looking at specific measures of oxidative stress in ME and LC cohorts. This study included testing interventions such as NAC supplementation (precursor to glutathione) to replenish glutathione and mitigate measured oxidative stress. The study includes a measurable intervention and outcome. Would RECOVER be open to replicating and further pursuing this avenue of research?" -elle seibert | got long covid?
- Is there anyone in this group interested in developing GPCR-AAb testing (G-protein-coupled-receptors anti Ab) and potential treatments. European CT with BC 007 neutralizing these Ab may have forthcoming positive results. Where can one find valid commercially available GPCR AAb testing in US? Cell Trend (Germany) may not be valid (?). -Megan McCoy

- I completely agree that the Compass-31 may not be asking the right questions. I have to answer those questions along with 3 other questionnaires every week with the Recover Vital trial. It is outdated and needs to be updated. -Christie Welsh
- MIS-C...Unfortunately, not so rare anymore: https://abc7news.com/post/sf-scientists-crack-case-severe-illness-put-children-deaths-door-after-covid/15166970/ -Zoltan Komar
- For Dr. Nath, Your T cell exhaustion data in ME/CFS patients is very interesting. Our group at Umass Chan has found CD8 T cell exhaustion by functional assays to be a common immunological finding and potential biomarker in both Long COVID and ME/CFS patients. This was also useful in our retrospective study with a nebulized antioxidant treatment, Inspiritol, as it reversed with improvement of symptoms. Do you have any other plans to try to pursue other treatments for T cell exhaustion besides check point inhibitors? -selinl
- MIS-C can also occur in adult too, especially the MIS Inflammations. Aren they not being tracked or considered for the adult? -Sonia Lee
- I encourage Dr. Nath, Dr. Randolph, Ian Lipkin, and others within NIH to study Droxidopa in combination with Spironolactone and LDN to prevent PEM in ME/CFS as well as Long Covid. Droxidopa prevents PEM when it is taken to treat the exertion, or in other words, when an exertion is planned and Droxidopa is taken during the exertion and for a time after exertion to the termination of the exertional recovery period. Daily Spironolactone and LDN work together with Droxidopa and are important as well. Unimaginable suffering is eliminated and quality of life returns. Stopping PEM stops the cycle of damage from exertion and allows the diseases to stabilize. I have +2.5 years of experience using these meds to prevent PEM. They are life saving in terms of reducing the suffering of patients. Dr. Nath's Intramural Study has proven a decreased level of norepinephrine in the brain, and this may be the basic science behind why Droxidopa prevents PEM. You are welcome to reach out. -Jennifer
- How many people in the US who got covid now have POTS? -destry
- The RECOVER sites don't even have doctors they can refer patients to. The Maine site doesn't have a single doctor in state to refer. Ppl are left going to Boston - provided they have time, carers, and financial resources. NIH needs to fix this. -Gillian
- MCAS seems to be the driver for many of Long Covid patients' multi-condition disease states. How much of a priority is looking into diagnosis, treatment and trials for MCAS? -Rebecca Letts
- Safety is always an issue and risk: benefit assessment is essential for any intervention. For someone who is extremely ill, the risk may be well worth trial. There are ways to mitigate infection risk. -Megan McCoy
- Reiterating because I think my question was buried among others: Dr. Nath, what pharmaceutical companies have you approached for partnerships, and around what drugs? You mentioned Bristol Myers Squibb if I heard correctly. -Rowan Walrath
- What is the NIH doing to pushed for the LC Moonshot Act to get approved in Congress? So we actually have enough funding to work on this? -Gillian
- Have you considered using this MIS-C technology in RECOVER? -Billy Hanlon

- with reinfections of covid and other viral illnesses trigger inflammation how do we advocate for ourselves. I was turned away from the ER until I had measurable respiratory issues. -Danielle Gillan
- Studies/research has showed that about 50% of Long COVID patients meet the criteria for ME/CFS when the months have passed needed for diagnosis. In fact PEM (post exertional malaise) historically been the hallmark unique symptom of ME/CFS until Long COVID patients were exhibiting it as well. So far I haven't seen a focus in the meeting on studying Long COVID induced ME/CFS as an important distinct subgroup. What has been done to study/identify this important subgroup in the LC population? -Amy
- The NIH intramural IVIG clinical trial is only a week. Most studies support giving IVIG for months to show any benefit. The RECOVER IVIG has a cruel exercise component. I would like to see a long term IVIG and SCIG trial that does not have an exercise component and has an open label extension, unlike the RECOVER trial. Can this be considered? -john bolecek
- Second part to my above question on MIS-C: (this new technology that would allow to look at the entire immune system's response all at once - has this been considered to use in RECOVER?) -Billy Hanlon
- And JAK inhibitors are now being trialed in PC that may help T cell exhaustion and ?? maybe micro-vascular endothelial damage. Used in rheumatology conditions with chronic inflammation. -Megan McCoy
- The virtual participants are being largely ignored during these panel discussions. Most answers are “sorry we missed your question; we’ll pass it along.” And virtual ppl are mostly patients. -Gillian
- I second a question that has gone unanswered in the chat - is there evidence that repeat infections make LC patients worse? -Gillian
- How can we best make sure that all researchers involved in future research are educated on ME/CFS? -Cynthia Johnson
- Dr. Lipkin, earlier this year you mentioned that this field could use better advocates. Do you mind if I ask what areas or sectors specifically could use better advocacy, in order to make the progress necessary? -Billy Hanlon
- Please address the importance of including pre-pandemic ME/CFS patients in future research. Thank you! -Cynthia Johnson
- Another objective CT secondary endpoint recommendation is to assess microvascular perfusion, tissue oxygenation or the primary determinant of oxygen delivery. (In clinical care poor-mans-test to assess perfusion time is to look for color to return to limb post occlusion with BP cuff…… anecdotally increased). -Megan McCoy
- It’s ableist and disrespectful that panelists and participants won’t wear masks to protect the very patients they’re working for. -Gillian
- How can we start to include many patients with ME/CFS under age 18 and over 65 as well as those who have been sick for decades? -Cynthia Johnson
- Would like if someone here was bold enough to say that the reason they are all there today is because COVID is a political talking point, and even to this moment, virtually the same illnesses (ME/CFS, fibromyalgia, chemical sensitivity, POTS, etc) are still being

ignored and don't have the funding long COVID has because they don't have the same political justification, even though the severity is the same. -Scott Daniska

- Home nurses to collect samples help with compliance and to keep patients in trials. Does increase costs however. -Megan McCoy
- Find pathophysiology and industry will follow. -Megan McCoy
- People are going overseas to try to replicate drugs that the US isn't expeditiously trialing. Similar to Dallas Buyers' Club, we have a situation like HIV/AIDS. When will the government make a commitment to expedite this endeavor? -Gillian
- Has a trial to prevent worsening of Long Covid been considered? If repeat infections may be worsening Long Covid, why are prophylactic monoclonal antibodies (like Evusheld, which is not available currently, but a replacement is in the pipeline) not being considered to be offered to people with Long Covid? Why are extended courses of antivirals not being suggested/offered to people with Long Covid in the meantime? -Michelle
- A comment: the heterogeneity of long COVID has been discussed often today. In the past the heterogeneity of ME/CFS has been claimed to be a barrier to understanding it. But actually ME/CFS may be less heterogenous than long COVID, and as mentioned by Dr. Lipkin, ME/CFS research can thus be informative for those symptoms that overlap with those of many patients who have long COVID. -Maureen Hanson
- Watching this conference, I am having trouble focusing on the content because I am so troubled by the fact that many or most of the speakers, as well as many in the audience, are not wearing masks during a major Covid surge. I recognize that the NIH cannot mandate mask usage, but could the speakers explain how they are being researching an illness that they recognize is serious and frequently occurring, but not modeling a basic preventive measure? -Meredith Cricco
- Thank you, Alba Azola. -alexgressley
- Thank you for saying this! I've been fighting with my insurance because they keep refusing to cover prescriptions that my doctors want me to take. There's a huge disconnect between health insurance providers and doctors who actually treat patients, this problem existed well before Covid-19. -Athena McCrary
- Thank you, panelists. There is such a lack of awareness with even neurologists who should know dysautonomia is a biologically based disease. Patients with these BIOLOGICALLY based disorder(s) cannot wait decades for help. Remember that manufacturers are frequently willing to give free drug even for off-label use or through their foundations for low-income patients or anyone with insurance that won't cover. Helps to ask for patient assistance and help with paperwork. -Megan McCoy
- Have any of the panelists ever seen someone recover after 4 years? -Robin Jones
- Yes, please study PEM more! -Ann
- Alba Azola, Jaime Seltzer: I encourage you to investigate Droxidopa in combination with Spironolactone and LDN to prevent PEM in ME/CFS as well as Long Covid. Droxidopa prevents PEM when it is taken to treat the exertion, or in other words, when an exertion is planned and Droxidopa is taken during the exertion and for a time after exertion to the termination of the exertional recovery period. Daily Spironolactone and LDN work

together with Droxidopa and are important as well. Unimaginable suffering is eliminated and quality of life returns. Stopping PEM stops the cycle of damage from exertion and allows the diseases to stabilize. I have +2.5 years of experience using these meds to prevent PEM and stabilize ME/LC. They are lifesaving in terms of reducing the suffering of patients. Dr. Nath's Intramural Study has proven a decreased level of norepinephrine in the brain, and this may be the basic science behind why Droxidopa prevents PEM. You are welcome to reach out. -Jennifer

- Thank you for mentioning PEM, this is a very critical and debilitating part of long covid. -paulk
- Excellent comments on inclusion and priorities from Jaime, minus the propagation of "infection associated illness" term again, which the general patient population has cast aside because it dismisses millions of Americans who have gotten sick without an infectious event, and there was no recognition of any of them from this event today. -Scott Daniska
- Can you expand on the importance of PEM understanding in terms of possibly preventing permanent illness decline? -Cynthia Johnson
- Thank you, Dr Azola, for mentioning PEM as a much-needed study in relationship to LC. -Katie Gasemy
- Will you also send the Q&A? There are so many great questions and responses. Unfortunately, since I am on my phone, I am unable to copy and paste the entire dialogue. It only allows me to click one comment at a time. -Melissa Charles
- Can you comment on cerebral hypoperfusion as a key mechanism in MECFS, POTS and Long Covid? This has to be included in all Long Covid trials. -Svetlana Blitshteyn
- Thank you Hannah for your emphasis on PEM. PCPs do not seem to understand this. -Ann
- Dr. Nath mentioned PEM -- development of Hinxton scael. Dr. Rowe include PEM in slide. -Elizabeth Unger - CDC
- Pentoxyfilline may increase tissue oxygenation… used for PAD. Have only seen anecdotal reports of improving PEM (Germany). Does this make scientific sense considering microvascular endothelial damage… downstream effects? -Megan McCoy
- There are a lot of ways to assess PEM virtually without having to bring patients back in person. The RECOVER trials have actually done this with all trials via the DSQ-PEM electronically. -Sarah Jolley
- What COVID precautions are taken (or will be taken) at RECOVER sites to help ensure patients are not reinfected by COVID? Are masks required at all RECOVER sites? Are free N95 masks provided to patients? Does RECOVER encourage sites to improve air ventilation and filtration? Are any COVID precautions taken? How are COVID reinfections taken into account with studies? And how are COVID infections taken into account for any control group? -Myra Batchelder (she/her)
- How are studies being made accessible for severe patients? As someone who's bedbound, attending two full days of a study is impossible for me. -Shannan Riemer

- Just want to say how much I appreciate all the clinicians, patients and advocates attending and speaking today, live and virtual. The clinician researchers who pivoted in 2020 are all amazing.. thank you all. I only hope that I can see some treatments/ progress in my lifetime and if not, then for future IACC patients. (knowing it takes decades from bench to practice). Many thanks again. -Jennifer Minhas (she/her)
- What about vaccine induced injuries? Is this data being incorporated into these studies? Very similar outcome. -alexgressley
- Thank you, Jamie Seltzer, for being a voice for millions missing. -Katie Gasemy
- How can you do an exercise challenge without causing SIGNIFICANT harm for the folk with MECFS? I just want to understand. -PF Anderson
- My name is Juan Lewis. In April 2020, I was hospitalized in the Netherlands due to COVID-19. After a lengthy hospital stay and rehabilitation, I relocated back to San Antonio, TX. During this panel, one of the panelists referenced research from the Netherlands. My question is: Are long COVID symptoms similar in both the U.S. and the Netherlands? Every day remains a struggle for me, and before COVID, I led a very active lifestyle. -Juan Lewis
- Please add a bucket for neurological small fiber nerve damage > 70% PC and high in ME as well. -Megan McCoy
- Anecdotally, some patients diagnosed with MECFS who undergo surgical treatment for craniocervical instability are self-reporting remission of POTS and MECFS symptoms, including PEM. Some of the patients have been tested in the trials of 2-day CPET. Although a small cohort, having these patients retake the 2-day CPET after these surgeries may provide insights into PEM. e.g., Cardiopulmonary Exercise Test Methodology for Assessing Exertion Intolerance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6131594/ -Casey Shannon (she/her)
- neuro vascular endothelial damage documented by Lindsay McAlpine, Yale neuro-immunologist. -Megan McCoy
- RECOVER AUTO has a subset of patients with cerebral perfusion measures. -Sarah Jolley
- It would be great if there was a database where people who have recovered from certain symptoms could post what has helped them. I have found solutions to the majority of my symptoms, and it could help researchers, especially if solutions were crowd-sourced. Time is of the essence with this illness (I've already lost one friend to suicide) and we don't have time to go through all of the years of trial and elimination. This could give the researchers a jump on their research. We're four years into this. For me, it has cost over $300,000 in lost wages and hard dollar healthcare expenses. -KJ
- Could please write me the Gentleman's name who is talking now? Even in private. Thanks. -Zoltan Komar
- Out of curiosity - if patients consented, would RECOVER be willing to deep dive into PEM pathophysiology/studies with 2-Day CPETs (blood draws, imaging, etc.)? -Billy Hanlon
- Really appreciated that last speaker who commented! -Reda Rountree
- I'm hoping that my question above is addressed in some way. It was good to finally hear talk of ME/CFS and PEM at the end of the day. -Amy

- As a 3+ year Long Covid patient, I am so grateful for this day. Thank you!!! -KyleCreane
- Will there be Long COVID funding available by NIH or NIAID for researchers, that is outside of RECOVER? -Billy Hanlon
- Who was the woman asking for combo antiviral? -Amy Geng

Tuesday, September 24

- Information about the RECOVER biobank and data resources just mentioned can be found here, reposting from yesterday in the event there are new attendees. https://recovercovid.org/ancillary. -Marrah Lachowicz-Scroggins, NHLBI
- It is likely not medically relevant to distinguish between some of these phenotypes. Look at this page from OMF that talks about a study that showed thrombospondin mediates symptoms differences between brain fog and orthostatic intolerance. Unless you believe thrombospondin is responsible for underlying pathology, then it isn't relevant to investigate. https://www.omfcanada.ngo/study-of-thrombospondin-1/. -Scott Daniska
- Would it help, going forward, to involve listening professionals in RECOVER- TLC, given Dr. Baden's well-made emphasis on listening? I'm involved with the International Listening Association, which focuses on the research and practice of listening. I'd be happy to help people connect with ILA as appropriate. Website is www.listen.org. -Janelle Backman
- Will post-exertional malaise (PEM) be more of a discussion point today, given the vast importance of this phenomenon in LC & ME, if you know? Thank you! -Billy Hanlon
- I understand that you cannot mandate masks and that you are providing and encouraging participants to wear them. Since this is a section on patient perspectives, would it be possible for you to let the in person attendees know that as a person with long COVID, seeing the number of attendees without masks feels dismissive and borderline offensive, especially given that there are long COVID patients attending in person. I am not sure they understand how their lack of taking masking seriously comes across. -Wendy Shenk-Evans
- Good morning - audio is breaking up. -Amy Torres Best
- Hi, I am a physician with long covid. My primary symptoms are brain fog and muscle atrophy/muscle wasting. I don't have autonomic symptoms. I have had a full workup for muscle atrophy including EMG to rule out ALS and muscle biopsy and studies to rule out mitochondrial disease. Have you seen any other patients with muscle atrophy/wasting as a symptom of long covid. The muscle wasting isn't due to inactivity; I have continued to be active and exercise and do resistance training, etc. but the muscle wasting is progressing. -Tatum
- I reiterate from yesterday, the diagnostics and knowledge of PCPs of what to do is really poor and desperately needed. -IBekirov
- I agree with Billy. Post Exertional Malaise (PEM) should be the highest priority in future clinical trials. This should be implemented by selecting drugs to trial to treat PEM, looking at study design and end points as well (wearables, lumia etc.) -John Bolecek
- Is there going to be any shared experiences about strokes? I have had two since January and have not been able to get into Neuro at UCSF because I have been told they won't accept Long Covid patients. How do patients like me find neurology that can help? -Dara York
- Thank you, Josh, for speaking to the need for much broader awareness in the clinical medical community. Lack of awareness and knowledge in primary care and hospital

settings is a huge barrier to diagnosis and treatment and is extending suffering. -Peggy Jackson

- Thank you Dr. Blitshteyn for acknowledging the dismal and the denial in the wider population! -IBekirov
- I contracted C19 in March 2020. I suffer from brain fog, blurry/dry eyes, PEM, and intestinal issues. What is the probability of any treatment being successful over 4 years later? Thank you. -Theresa Lapsley
- Wow, my heart breaks for him. What an incredible story. Very thankful for his strength to come advocate today. -Scott Daniska
- Just submitting my comment for inclusion in the report: Alongside controlling for whether or not patients are experiencing PEM during measurements at trials, we need to also collect data on hormonal levels, and potentially fluctuations, occurring during PEM. The speakers in the NIH roadmap group for 'other conditions' are likely to be able to provide more advice on what may be relevant here, and patients who menstruate can provide more detail on potential hormonal trends that should be controlled for in clinical trials. Thank you. -Emma Barratt
- One symptom we have not heard about is the terrible destruction of our teeth, which many Long Haulers experience. I've always taken excellent care of my teeth. However, since developing LC 20 months ago, I've developed chips on several teeth; multiple crowns have fallen out, and my teeth are MANY shades more yellow than just prior to LC. I suspect chronic dry mouth (another thing we've not heard about here) is a major driver of this destruction, but I suspect there is some other LC-related cause. I ask the RECOVER-TLC Executive Committee bring in participation from the National Institute of Dental and Craniofacial Research. -Allison R.
- Hello, my note is related to symptomology that has not been included in trials to date. Severe neuropathic pain, soft tissue inflammation, MCAS related allergenic reactivity, joint and muscle pain to the degree I am often unable to get out of bed. Inability to eat most foods. I often feel that because these symptoms have not been a part of trials, I must be one of a minority suffering from these issues. Hoping there will be discussion in new trial development to address these symptoms. Thank you. Sachi Ushihara
- Thank you, Jermaine, for sharing your truth and for all your advocacy. JD Davids / Long COVID Justice
- Thank you, Jermaine. We see you; we hear you! Xxoo. -Rivka Solomon
- For those asking for PCP education, the ECHO Project at iecho.org offers educational sessions directed at PCPs about Long Covid. -Michelle Winer
- Totally agree with Rivka Solomon. -IBekirov
- Not all cases of long covid are equivalent to ME/CFS. I have brain fog and muscle wasting. No POTS, dysautonomia, PEM. Don't forget those of us who have different symptoms! -Tatum
- Great presentation, Rivka! -Anna Gil
- To verify my statements from yesterday, this morning I ran a community poll online asking people with ME/CFS whether they had an infectious event at the onset of their condition. 43% of patients reported no infectious event, yet I have only heard all these

advocacy leaders advocate ONLY for the 57% that did. We should not be stepping over one another for research funding, we should all be working together to get treatment for EVERYONE. I continue to not hear a single speaker acknowledge this massive 43% of patients with no infectious initiating event. -Scott Daniska

- A lot of excellent medication education on Long COVID and ME/CFS is found at the Bateman Horne Center: https://batemanhornecenter.org/ -Rivka Solomon
- Thank you for reminding everyone that clinicians need to learn more to "avoid causing harm" -Ann
- @EzraSpear: BRAVO! -Allison R.
- This patient perspective was powerful and inspiring! -IBekirov
- Yes Rivka, NIH needs to hear ME/CFS patients and scientists who work on ME/CFS! -aslann
- Great statement, Ezra. Totally agree, we need to try interesting drugs like DextroNaltrexone. Will the Agenda allow feedback from patients on what drugs they want trialed? -John Bolecek
- Unfortunately, the current RECOVER clinical trials are trialing things us patients have already tried and haven't worked like exercise, melatonin, pacing, and sleep hygiene. How can we ensure the new trials try better drugs? -John Bolecek
- Thank you, Dr. Zimmerman! Patients have had a voice in RECOVER trials. -Marta Cerda
- To add to the excellent point on checking patient nutrient status: Some research has shown that some nutrients are depleted in the spinal fluid, but not systemically. There is recent work showing b12 is depleted in the spinal fluid of those with long covid, whereas it appears at typical levels in the blood. Consideration of this dichotomy would be important to consider when designing research on nutrition/nutrients. The speaker focusing on the spine in the NIH MECFS Road map's neurological working group is aware if this work and may provide further advice about controlling for this in clinical trials. -Emma Barratt
- Thank you, Ezra, for speaking for so many of us. -Rivka Solomon
- The most immediate path to improvement in quality of life for patients is literally just simple surveys. Why has the NIH not surveyed the patient population across a variety of treatment options, and weight the outcome (beneficial or harmful), to compose a list of recommendations for treatments that are most likely to be beneficial and can be ranked most to least beneficial. This could be done within a matter of DAYS with zero funding, distributed to doctors across the country and lead to immediate quality of life benefit. Why has this not been done??? -Scott Daniska
- Can Dr. Zimmerman expound on how they are limiting patient visits? The RECOVER IVIG trial requires weekly visit for a year and there is no open label extension. A drug like SCIG could have been chosen which can be administered at home. -John Bolecek
- I strongly agree with Allison R. that having dentist involved into research and care into Long COVID and ME/CFS. After a severe relapse in my ME (which I have had for 50 years) following COVID vaccine I developed dry mouth which resulted in worsening of my chronic dental disease where I had resorption of multiple teeth. After this relapse I have had to have to have 6 dental extractions. All these teeth had resorption; a

condition poorly understood. These are not trivial surgeries as I have severe TMJ and must hold my jaw during surgery, so it does not dislocate. But I also developed a severe submandibular salivary gland infection which took 3 months of antibiotics to resolve. I am fortunate that I have a wonderful dental surgeon, who is learning about dental disease in ME and Long COVID with me and works with me. She recently recommended a new product Stellalife VEGA Oral Care Recovery Kit, with mouth rinse, gel and spray. This has greatly helped better control my dry mouth symptoms. -selinl

- I agree with Wendy. It is disheartening to see the attendees without masks. It is echoed by experience trying to access care. Long COVID clinics should be safe spaces for those who have been impacted by this nightmarish disorder. Not doing so is ableism. -Cindy
- Why weren't some of these trials open to pediatrics? They could easy have participated in some of these trials. -Megan Carmilani
- What effort, if any, is there for looking at (performing clinical trials or case studies) using functional medicine nontraditional treatments such as ivermectin, fulvic acid, blackseed oil, and other treatments aimed at clearing spike proteins and inflammation? I would like to encourage out of box thinking for treatment that will resolve patients' syndromes rather than band aid treat symptoms. Thank you. -NANCY
- Thank you to everyone who is masking. It's not just a signal that you are following the science on LC prevention - information that so many are not able to access due to widespread misinformation and disinformation. It's also literally putting science into action to prevent our reinfection which could set us back further. It makes a huge difference to us. When you choose not to mask, it is a form of gaslighting when we struggle every day to avoid reinfection. It is a matter of trust and the realities of asymptomatic COVID transmission, not theater. It is no more about individual choice than having a shared expectation that people in the room will not be smoking, whether or not they'd choose to do so otherwise. -JD Davids / Long COVID Justice
- For those who took Paxlovid and got a rebound infection and now have long COVID, is there evidence that while Paxlovid can help prevent long COVID, do those who get a rebound infection have equal or greater risk of long COVID? -Wendy Shenk-Evans
- Agree with Nancy that functional medicine needs to be included. -Wendy Shenk-Evans
- I have heard from multiple RECOVER participants who noticed that there was no tracking of medication changes over the trial. They attempted to share these changes with staff but do not believe that this information was integrated, and they are concerned that this means that changes in their symptoms or objective findings that were due to medications were not properly understood. Will study designs going forward include collection of medication changes and analysis of potential impact? - Meredith Cricco
- I urge research to still consider PAX to treat LC. Timing and duration of treatment is a possibility in not seeing the effect. Furthermore, there might be benefit in only a subset of patients with LC depending on currently unknown and mulitple factors. - IBekirov
- There are more than 100 clinical trials for long covid on Clinical trials.gov. why were only 2 discussed? -dichter

- Also, combo anti-viral therapies should be tested in LC CTs moving forward. -IBekirov
- It needs to be noted that the improvement in the null arm is not necessarily placebo. ME/CFS patients have reported intravenous saline as one of the most beneficial therapies, it is a treatment for orthostatic intolerance. -Scott Daniska
- Hi, Its so hard to listen to her. Thanks. -Nandini B Raj
- This is to the post from "Tatum" about muscle wasting. Yes, I have experienced the muscle wasting and the IVIG treatment have helped. However, the CFS, PEM, IBS, Brain Fog still remains along with body's low tolerance to stress, etc.- -Sonia Lee
- in the paxlovid study were you able to do a post hoc analysis to see if there were biomarkers predicting response in the subgroup that did improve (e.g. spike protein ag assay)? -Nancy Klimas
- I agree with the others who are commenting about the use of masks. They should be required for a meeting about an illness that is caused by breathing in a virus in wide circulation. Leading by example as some are doing is much appreciated by those of us suffering from long covid and trying to stay safe. -Claire
- Are there any plans to carry out a similar trial to STOP-PASC but with a longer course of paxlovid? -Hannah Nicoll
- For inclusion in overview: 2 years into my long covid, I haven't seen much about changes in vision but one of my major symptoms is opthomological-I lost my binocular vision which took a long time to diagnose, and the resulting headaches greatly contributed to 'breaking' my brain. I was lucky to connect with a neurological ophthalmologist, Dr Don Lyon, with IU school of ophthalmology who shared he has worked with >200 LC patients who have vision problems. He listens, believes and supports me. He was helpful when I was denied disability for my PRIVATE PURCHASED disability insurance through my employer. It is important to educate the different types of insurance ie health, disability and life so patients can get the support they need and deserve. -Linda Patton
- When diagnosing patients with Long Covid, PEM must be sought by default. The subgroup with the ME/CFS is otherwise doomed to worsen with every crash up to bed rest. Early diagnosis is crucial to maintaining at least a little bit of QOL and the ability to work. Thank you. -Johanna Borde
- As a patient who has tried a myriad of treatments I can say the placebo effect is huge!!! We are soooo desperate for any improvement that we hyperfocus on trying to notice any slight improvement while starting a new drug. THIS IS OBVIOUSLY WHY BIOMARKERS ARE PARAMOUNT!!! -jeffrey Hamilton
- Will recordings be posted? I missed yesterday afternoon's sessions. Thanks. -Simmon
- Can Dr. Eldrin Lewis share why assessing/monitoring PEM is very critical in any of these clinical trials? -Billy Hanlon
- Thank you to Upinder Singh for mentioning the fact that Long COVID (and ME/CFS) patients can become hypersensitive to medications and all interventions. -Rivka Solomon
- Thank you. -Nandini B Raj

- From what I know Paxlovid temporarily makes the body feel normal for a short time until a relapse occurs or a re-infection. Perhaps something to note. -Nandini B Raj
- Pfizer is supposed to have a new version of paxlovid coming out without all of these interactions though unsure of the timeline. Has anyone at NIH been working with Pfizer to ensure we are combating misinformation like paxlovid rebound, especially in immunocompromised people, and what are we doing to educate clinicians on viral persistence and needing antivirals during acute infections regardless of health status or acute case severity? Combat the misinfo/ alerting clinicians to safer methods. -Karyn Bishof
- Reinfections with COVID-19 have been reported. Do these represent new infections or viral reactivations in particular individuals? -Isabel Silvestre
- I surveyed ME/CFS patients before the pandemic even started and larazotide acetate was one of the top treatment outcomes reported from the community, meaning in patients without spike protein. -Scott Daniska
- i am not sure about any other patient's views, but I am leery of studies that are funded/supported by pharmaceutical companies. I believe there is inherent bias in these studies, even if those performing the study intend to be unbiased; I intend no offense here. I would like to see studies that are funded by other means. Thank you. -NANCY
- https://rally.massgeneralbrigham.org/study/pediatric_long_covid_clinical_trial. Link to larazotide study for kids with Long COVID (includes screening test for Spike for enrollment). -Dr Lael Yonker
- Are the study controls COVID19 vaccinated or not? -Isabel Silvestre
- Amy Proal, amazing idea, just amazing. When I received Evusheld, it helped with so many of my Long Covid symptoms. -Michelle
- Hurray Dr. Proal!!! Your passion in working to cure this really shows through! Wish others at NIH were likewise. -Jeffrey Hamilton
- Could the NIH send LC patients a survey to see who/how many folks would be interested in specific treatment trials such as e.g., the monoclonals Amy Proal is discussing? -Katie M.
- We published a paper demonstrating reductions in neuroPASC symptoms with early monoclonal therapy. Such a good idea to trial the older mAbs on PASC from earlier variants. https://pubmed.ncbi.nlm.nih.gov/38516779/ -Sarah Jolley
- Just wanted to say thank you to Dr. Singh for the team's hard work on the STOP-PASC trial - I was a participant and I am proud to have participated. -Ezra Spier
- Why do you think IVIG would be helpful if it is not specifically targeting Covid antigens? Focus on more specific therapies. -Jeffrey Hamilton
- Dr. Upinder Singh and all speakers: Will there be clinical trials that include pre-pandemic ME/CFS patients? We can't abandon those of us (like me and millions more) who have been sick for decades before the pandemic. Thank you! -Rivka Solomon
- When I fell ill with Long COVID, it took over 6 months to get a diagnosis. Though I had no known health conditions, I discovered reactivated EBV, cytomegalovirus, Lyme and many other viral or endotoxins in bloodwork. Have any of your trials addressed the

connection between SARS infection and other viruses or endotoxins in the body? Will this be addressed in future trials? -Ylan

- Please repeat the name of the drug being evaluated that impacts gut permeability mentioned by Amy Proal. -Penelope (Penny) Markham
- When using antibody-based treatments for COVID19 infection and long COVID, ADE may cause the illness to worsen. -Isabel Silvestre
- @tatum If you want ideas re/ your muscle wasting, I might be able to help. My email is public. -Susan Kandarian
- Before each study, please determine which Long Covid subtype the participants are to be assigned to. The study results will then show which subgroups, which therapies help. The study results then become comparable and can be brought together. Please see the work of Prof. Moreau. https://youtu.be/dWeKObi1o1o?si=Kehj5tMFUUr2au-y" - Johanna Borde
- I want to reiterate what others have said about studying PEM and not with exercise that is actively harmful for MECFS patients. This is known. Again, the NIH needs to confer with the MECFS medical community! -Sara
- My vision has also been impacted. After having Covid in Sept/Oct 2020, I noticed vision changes and in Feb 2021 was diagnosed with Wet Macular Degeneration, inflammation of the blood vessels related to my retina in my left eye at the age of 61 (which I understood was early). I also have significantly blurry vision and dry eyes. Though my vision in my right eye has not changed, I have more trouble seeing because of this. So far my eye docs have poo pooed the idea that this is related to Covid. -NANCY
- Thank you, Amy Proal! I appreciate (and am not surprised) from the research and directions forward from my alma mater! IBekirov
- Why doesn't the NIH just give significant funding to the passionate researchers (Proal, Peluso, Iwasaki, Pretorius) to run meaningful trials by now. Please stop wasting money on trials that do not move the needle. -Jeffrey Hamilton
- Are the biosamples that are collected being timestamped? That is important to understanding/interpreting the data in the context of circadian rhythms which may influence results. -Lisa Cash
- The question was more about whether when patients have a rebound infection from Paxlovid are they at increased risk of long covid. -Wendy Shenk-Evans
- Are there any plans to extend the VITAL trial past 25d given what Peluso mentioned earlier w/ the cat model? i.e. to adopt the "adaptive clinical trial" model first proposed?" -Jon Douglas
- There are many interesting approaches and study designs, but experiences in other fields have taught us that there is great value in supporting interventions not selected by RECOVER TLC. What mechanisms do you propose to fund those? -William Hu
- also could the US government or big pharma sponsor more of these trials with their existing pharmaceuticals? mAbs have been on shelves for a while, Klimas was unable to get access to earlier ones due to them not cooperating. same with UCSF. do we have to wait for pharma to collaborate to make progress in science here?" -Jon Douglas

- I've had POTS since my infection 2020. My standing HR has been well controlled w meds so orthostatic vitals do not always work for objective measure of POTS. I showed +QSART but did NOT have cranial blood flow test. Could blood flow be an option for dysautonomia study outcomes, perhaps when studying IVIG or immune modulators? Why or why not? -Jennifer Minhas (she/her)
- Is anyone tracking HRV through wearables in current studies? -Anna MacKay-Brandt
- And NIH should give to the Selin Lab at UMass Chan Medical School, as they are investigating a potential T cell biomarker. -Rivka Solomon
- I tested positive for Covid Christmas Day 2021. In addition to pneumonia (that required 10 months of low dose steroids), steroid induced diabetes, dysautonomia, neurological issues, chronic fatigue and pain, tremors, severe leg cramps, I have also developed avascular necrosis in both hips and left shoulder. Is anyone looking at a correlation to inflammation and AVN? -Melissa Charles
- Comment- Safe rehabilitation-based trials are more symptom management versus targeting the root cause. -Nandini B Raj
- Would RECOVER consider utilizing the invasive 2-Day CPET to deep dive on PEM, like the Brigham and Women's Hospital team is undertaking with Dr. David Systrom? -Billy Hanlon
- Is there a place where we can view the NIH's basic science studies related to Long COVID? Or can we get a list of ongoing basic science work being done that's focused on Long COVID? Thanks. -Douglas Lindsay
- The LIINC studies have started providing rides (via Lyft) to study visits and it has been hugely beneficial for my participation in research studies. I'd suggest RECOVER consider providing these logistical supports as well. -Ezra Spier
- We need specific blood based, objective biomarkers, not subjective or wearable devices. We all know meaningful objective biomarkers can be discovered utilizing the exquisite molecular technologies available today. -Jeffrey Hamilton
- I live in Pittsburgh and have begged for IVIG. I cannot drive and I cannot travel far. Please make this trial available in Pittsburgh. -Sarah Majer-Powell
- Patient feedback was used for RECOVER trials. I was on the RECOVER Vital team, for example. -Marta Cerda
- After everything you've heard over the last two days, how many of these trials do you still feel are appropriate? Would it demonstrate RECOVER's adaptability and ability to pivot based on new data to redirect some of the funds for goal-setting exercises and brain retraining programs into Dr. Nath's terrific idea for a checkpoint inhibitor trial? -Duncan
- To add to the mask discussion. Every individual has the right to decide when/where to mask, however all doctors and researchers working with patients with Long Covid and IACCs should create an environment in health care/research setting where they are at the least mask friendly. Better yet, if I volunteer my time to be in a research/clinical trial or bring my child for an in-person study, everyone I encounter should be willing to wear a high-quality mask. Especially if I call ahead and ask for this. It is extremely difficult to navigate in-person health care with a child with Long Covid. Recently I was asked at a

pediatrician appointment if we were masking due to a recent infection. I know families that are hesitant to participate in the Pediatric RECOVER Tier 2 study because they do not want to risk another infection. -Amy Torres Best

- For all of the RECOVER trials already underway or upcoming, can you please require masking (better, use of respirators) to ensure safety of participants? It's about avoiding reinfection, validating science and our suffering, and not triggering PTSD for many. Thank you. -Katie M.
- Will you still require initial PCR positivity for ongoing trial enrollment? You can get many, many more participants if trials were open to individuals based on clinical findings without PCR testing necessary. -Jeffrey Hamilton
- I completely agree with the pediatric neurologist who spoke as a care giver for her daughter that Long Covid and ME/CFS are immunocompromised due to their T cell exhaustion (Gil et al. 2023, Brain, Behavior and Immunity_ Health) and other immunological dysregulation which has now been clearly shown by our group and many others including the NIH study presented by Dr. Nath and published by Dr. Iwasaki and Dr. Grimson and Haansen. Unfortunately, this has been under appreciated. These patients should be approached and treated for any infection like any immunodeficient patient. This is an easy and very important message that can be gotten out to the medical community and there is a great deal of experience in treating immunodeficient patients from all the experience and studies with HIV patients. I am disappointed in how little discussion there has been so far at this meeting on reactivation of persistent viruses like all the herpes viruses (EBV, CMV, VZV, HSV and HHV6) and retroviruses like enteroviruses. -selinl
- It should be clarified that the usual care arm in AUTO is not a non-therapeutic placebo, but weekly saline infusion which can be a treatment for post-COVID POTS. -Sarah Jolley
- In June, Dr. Al-Aly (one of the speakers yesterday) and colleagues penned a Medscape piece advising 4 recommendations to improve RECOVER (Improve Coordination, Move Beyond Symptom Management, More Clinical Trials, Take the Focus Off 'Soft Therapies). How receptive has RECOVER leadership been to these recommendations? -Billy Hanlon
- What are other known reservoirs for SCoV2 besides the gut and lymph nodes? Can it be practically everywhere in the body? -IBekirov
- I can get to a Pittsburgh hospital. Biopsy all you like. -Sarah Majer-Powell
- How are researchers including bedbound patients? Are severe cases being considered? Do mobile labs exist? Also, to prevent reinfection, are all participants and researchers in your studies required to mask? -Shannan R.
- Thank you for mentioning EBV reactivation. A functional medical doctor raised this as a possibility and my POTS specialist said that reactivation is not a thing. Is there someplace to see information on this from research? Also any links to research regarding GI long COVID issues and testing that should be done? Thank you. -Wendy Shenk-Evans
- I think it is important to understand the key pharmacokinetics and pharmacodynamics of each of the major interventions. For instance, I could find very little data of the CNS

pharcokinetics of paxlovid in humans. Also, the dose and length of therapy is being pulled out of the air based on treatment of acute disease. -Benjamin Luft

- I appreciate Dr. Zimmerman mentioning that it's important not to unintentionally set patients into a relapse as a result of the clinical trials. I want to mention that I'm a patient participant in the RECOVER observational study, and at the location I go to, there really has not been enough care taken on that front. I have been thrown into PEM multiple times because of the study conditions. I don't have a question, but I did want to mention this because it has been frustrating and it's something that really should be attended to in both the observational and interventional studies. -Lila
- Is there any interested to include LDN and Low dose Abilify? the potential mechanism are anti-inflammatory and immuno-modulator. -Hector Bonilla
- Dr. Yonker - I will share the trial in the pediatric Long Covid Facebook groups I am active in. I have not shared it in a few months. -Amy Torres Best
- Preliminary data for our institution (Stanford), found some cell types are involve in patient with Long Covid (monocytes, platelets, NK cell etc.) by using Extracellular vesicles analysis. Is any interest to look at this method to classify patient and direct therapies. -Hector Bonilla
- Does the NIH plan to employ a dedicated team to running, coordinating, assisting TLC trials? -Katie M.
- What is thought to be the improvement rate of long-COVID patients (from trials) with time and no intervention? Natural history of long-COVID? Are there any biomarkers from the studies that showed we can identify these patients who may recover naturally? -Frances Eun-Hyung Lee
- Drs. Peluso & Proal are ONTO SOMETHING VALUEABLE with the viral persistence...They should receive every possible resource...Mark my words on this... -Zoltan Komar
- Today, have the PCPs, PA-C, or Specialist have started to test patients for the broad infectious disease, inflammatory, pre-cancer blood tests at initial intake to see the broader and comprehensive view of the patient yet? This is to address the heterogenous nature of the Long-Covid and asymptomatic issues it present. -Sonia Lee
- There is a large infrastructure with established contracts under DCRI, I hope that RECOVER-TLC can preserve that infrastructure with the new scientific ideas for clinical trials that can be operationalized. Suggesting this as request to preserve an established clinical trial network rather than to build a new one from scratch. -Sairam Parthasarathy
- Do we have well defined patient cohorts from clinics that can be used quickly and effectively for research. Instead of each study having to recruit and screen patients each time and have (as it sounds) to recruit them remotely (i.e. the 2 hours drive). -Annette
- What's the plan after this conference? Is there a follow-up, or are we waiting another year for any infrastructure changes to happen? Shannan R.
- Is this not a question to ask? I did not get an answer: Is there a place where we can view the NIH's basic science studies related to Long COVID? Or can we get a list of ongoing basic science work being done that's focused on Long COVID? Thanks. -Douglas Lindsay
- Here is a list of the current pathobiology studies and PIs https://recovercovid.org/pathobiology. -Marrah Lachowicz-Scroggins, NHLBI

- Re: the question above from Douglas Lindsay about LC research currently funded by NIH… A very good info source is the NIH RCDC page (Research, Condition, and Disease Categories). https://report.nih.gov/funding/categorical-spending#/ -Michael Sieverts
- I agree about having more telemedicine. Standards of care do not differ by state, each physician takes the same boards, unlike law licenses. If it is a money issue, the fees could be pooled for licensing nationally and distributed to each state based on some kind of formula that is proportionate to the amount of funding each state receives currently. -Martha
- Would be interested in whether heart rate variability is being collected and available for researchers. -Anna MacKay-Brandt
- As a patient, I did see protocols and could comment on them. Again, my feedback was heard. I know other patients were able to be heard as well. -Marta Cerda
- Is it possible to mute the mics during break? Thanks. -Holly Latham
- Maybe turn off the mics during breaks and lunch? -Lila
- It's essential to ensure your websites are accessible to people with disabilities. This is a barrier. Please review ADA guidelines before launching any surveys or sites. -Shannan R.
- Just want to express gratitude to everyone presenting today. -Danielle Gillan
- Please make sure the sound gets turned back on. -Alison Cohen
- Is there going to be a trial focusing on (systemic) inflammation? Also, is there a trial for metabolic problems and weight? -Katie M.
- For 2 years I've had autonomic dysautonomia with orthostatic hypotension due to long covid. A neurologist suggested that I consider a 3-week course of prednisone, but I've been reluctant to do so knowing that long covid is already associated with immune dysfunction. Can any of the researchers (Dr. Svetlana Blitshteyn?) address whether corticosteroid have been found to be helpful in reversing long covid autonomic dysautonomia? If so, what/how strong is the evidence? References? Thanks! -Diane Ramus
- After all of these "root cause"/mechanism discussions are great, but I haven't heard anyone discuss environmental factors. Long COVID patients are found to have impair barrier integrity, affected liver function, impaired lymphatics, exhausted immune system, slow wound healing/repair mechanisms, altered antioxidant profiles... ALL of which affect the body's ability to protect and process environmental insults. I have seen in countless patients, reports of improvement when moving to better air quality, and worsening in condition when exposed to cleaning chemicals and the like. -Scott Daniska
- Was there an Intervention Options slide 3 of 3 we can see? -Michelle
- Will there be a researcher intervention list from the researchers in the room too? things they haven't been able to get to? -Jon Douglas
- what is link Dr. Vogel was talking about? -Robin Jones
- Please encourage speakers to share their presentations and recordings. I am unable to watch all sessions. I could not type fast enough to capture all that Dr. Vogel just shared. -Amy Torres Best

- Julia Moore Vogel's talk was excellent because it is concrete and gives us a concrete roadmap of what we can trial. Thanks to PLRC for that list of potential interventions. -Rivka Solomon
- So many options for repurposing. After being in the Yale Paxlovid trial and assigned to placebo (which wasn't really placebo because I received Ritonavir), I realized that the Ritonavir really helped, and the Stanford trial results reflected this—both groups improved. I am now on Ritonavir and finally improving after 4 years of illness. -Amy Engebretson
- Can we make therapeutics used in Europe easier to be included in clinical trials in the US? Why treat therapies used safely in Europe from being included in Long Covid clinical studies in the US. A perfect example is immunoabsorption technology to remove pathologic antibodies, immune complexes, cytokines, etc. -Jonathan Dinsmore
- Thank you, Michael and Lizzie, for sharing the links to look over pathobiological studies and the NIH report. I will take a look at both links. And If you or attendees or organizers have any others, I'm interested to see them. :) -Douglas Lindsay
- Agreed. Julia Moore Vogel nailed it. Please lean in on her guidance. -Shannan R.
- Can non-US-based users contribute to CURE ID? -Emma Barratt
- How much beta testing by actual participants occurs before an online survey is rolled out? -Martha
- Q: Does CURE ID plan to work with the FDA to expand access to many of the interventions discussed in this conference so patients and their providers can report outcomes for hard-to-access interventions? -Jon Douglas
- Would love if someone brought up how poor pharmaceuticals are in general. Vast majority of patients experience a whole host of long-term side effects from them, even if there is a benefit to a particular symptom. I would like to hear someone advocate for 'removal therapy', instead of advocating for adding more toxins to the patient's body. Jarred Younger just released evidence that PM10 and AQI strongly significantly correlate with fatigue and pain in ME/CFS, so where are the healthcare professionals advocating for improvement in air quality to lessen symptoms? https://youtu.be/oUxUg3GciJY?si=lOwaoNgZ8wSsOS8S&t=758" -Scott Daniska
- Question for CURE ID, is it possible for participants to list treatments OTHER than drugs? -Dana Dharmakaya Colgan, PhD, OHSU
- Maybe I just couldn't find it but I didn't see ME/CFS on the CURE ID website. It would be a shame to leave this cohort out when they've likely tried many more things over decades of post-infection disease. -Corinne Dorfman
- How can we get the QR code to share on social media and within groups . -Danielle Gillan
- Can you also gather safety and tolerability information Heather? Even if briefly. (and dosing if not already included). TY for your work on this! -Megan McCoy
- With new COVID variants developing every ~4 months, how can treatment strategies and Clinical Trials keep up with a rapidly mutating virus and the global population not serious in containing the virus with at least masking protections? -IBekirov

- For Heather Stone: Thank you for sharing more about CURE ID. Is this the main way the FDA is learning about what drugs are being used successfully or unsuccessfully off label for Long Covid? -Michelle
- Why does the CURE ID system ignore the possibility of a therapy (vs. a drug) being effective for Long Covid? (Besides that this seems to be an FDA system...) -Chris Wikman
- Do you think that a diagnostic biomarker would be necessary to achieve valid results and convince investors, especially when it comes to MEC/CFS (aka PEM)? -Johanna Borde
- I heard yesterday about potentially needing controls who believe they have never had Covid because former controls have become infected. Is there a place where potential controls can register to participate in trials? -Martha
- How would we submit a request to test a biomarker? -David Vera
- Will this RECOVER TLC Intervention form have definitions or an "i" info button to help users while they answer the form? Especially helpful for brain fog and cognitive issues to have clues or explanations (e.g., biologic, or small molecule what are those). Thanks. -Katie M.
- Are there any potential VC funds for pilot studies of new rx (given industry seems slow to pick-up funding until there are identified known patho-phys)? -Megan McCoy
- Can you please clarify when this will be live and what the timeline is for submission? -Rachel Hess
- Who will comprise the review panels for these submissions and how will that process be completed? -Sarah Jolley
- Does the NIH / Foundation have a list of therapeutics proposed similar to Vogel presented? -Jon Douglas
- What are the best tools (validated) to collect severity of overall illness, cognitive functioning over course of time? Is COMPASS validated? TY. -Megan McCoy
- When employing neutralizing abs in vaccinated long-term COVID patients, what are the patient criteria and considerations? -Isabel Silvestre
- DIY project for patients - what a great comment! -Ann
- From a patient perspective, Recover Trials need to have more urgency, more pharmaceuticals, and unique interventions (see Dr Vogel's list, Dr Buchman's list etc) (we can do pacing, mind body work, PT, supplements, breathing exercises, etc. on our own), and reach patients beyond the Recover Sites / surrounding community. Also from a patient perspective, this 3-day collaboration and sharing could not be more worthwhile. It is one of the best things Recover has done, to set up public collaboration and feedback sessions. THANK YOU to every single person who helped to put this together, who has presented, and shared information, and to all who are listening, thinking, and taking action. Thank you. -Michelle
- Is the submission portal active? If so, how can I access the form? How do I access the portal that you were talking about? -Robin Jones
- Meighan makes an amazing point. Same point that Dr. Ziyad Al-Aly made yesterday. Listen to your patients. especially in conferences like these ones. -Dori DataBae

- YES. -Danielle Gillan
- How long will the portal be open once it is live? -Rachel Hess
- THANK YOU, Meggan! -Dana Dharmakaya Colgan, PhD, OHSU
- I belong to a LC Support Group with 67K members around the globe. Everything I know about LC I have acquired from community there or began with a kernel of information from them. What a rich source of data for researchers. Happy to discuss offline: allisonrosenberg@live.com. (I hope providing my email address doesn't break some rule). -Allison R.
- Sorry if I missed it, but could someone please explain if the CURE ID entries are different than the upcoming TLC intervention form Stacey covered? -Katie M.
- + 100 to Rachel. This meeting is important and seems very light on what is needed for children and adolescents. -Lawrence Kleinman
- I hasten to add that many of us have advanced training in science, medicine, and research. -Allison R.
- Caregivers are not care partners so that is problematic language. -Lawrence Kleinman
- Given the variability of patient's symptoms, what is the minimal number of participants & randomization ratio, to be able to detect any meaningful biomarker information/subpopulation effect? Dr. Vogel proposed 100, is it widely accepted? Any lessons from ACTIV? -Florence Herschke
- Is it possible to add gender to data collection tools given Nath's ME phenotyping Feb finding T cell exhaustion in males>> females. -Megan McCoy
- Q: to Timothy: do you have any personal perspectives on likely ACTIV agents that may work in long covid whether longer duration monotherapy or in combination? -Jon Douglas
- There desperately needs to be more access to Long COVID treatment centers and dissemination down to PCPs. -IBekirov
- In response to broader education…. go to UpToDate writers to write up to date guidelines. I see areas that need current information. Publish basic information in the AAFP and other journals, e.g. pediatrics, etc…. -Megan McCoy
- How can I find information about managing long-COVID symptoms ex: increased symptoms of ADHD? -Cheri
- The Sick Times and Long COVID Justice are releasing a series of online and printable resources on Long COVID Essentials. They are brief but are designed for patients to take to providers, among other uses: https://longcovidjustice.org/long-covid-essentials/ -JD Davids / Long COVID Justice
- are there options to have a list of COVID Clinics in each state that may help patient's get better access that they are unaware of? -Janice Stout
- Is there a one sheet overview of long covid that I can give my primary care to help them understand what they need to look at re LC? -Linda Patton
- Could the current/upcoming data collection tools collect practicing providers who are astute and helpful. -Megan McCoy
- Can we stop with the "rich white folks" racist aspersion? Many people are NOT rich, on Medicare, and if they are in the right area can get care. -Rob Perkins

- Thank you for the discussion around awareness. I'd like to add that many (or all) of the resources now are one's physicians must seek out, therefore they are already aware and interested. Is there discussion of mass communication efforts? We need push strategies as well as pull strategies. -Peggy Jackson
- Will the wearing of N95 or better respirators for any patient contact for trials be built into the protocols? -Martha
- Do you have a target number of antivirals, versus immunomodulators, versus mitochondrial modulators, versus thromboembolism modulators... that RECOVER-TLC would test? -Florence Herschke
- I would encourage that the expert panels include clinicians who are actually caring for patients with Long COVID not just potential scientific content experts as many active Long COVID clinicians know these challenges that their patients are facing and what they have tried successfully and unsuccessfully. -Sarah Jolley
- Other ways to educate free CMEs, continuing medical education for credits for re-licensure; Grand Round speakers; Lunch time talks. -Megan McCoy
- Can cost-prohibitive (for patients) treatments that have already been studied and shown benefits plus have individual anecdotal data are helping be prioritized or fast-tracked? Hyperbaric oxygen therapy/HBOT comes to mind. Insurance won't cover these because it isn't FDA-approved for LC, and hospitals are denying patients to even try HBOT *out of pocket* because of Medicare not paying the hospitals in the past. There aren't options for patients to try HBOT despite the fact that it has been shown to give people their lives back or even just greatly reduce some of the most burdensome symptoms like fatigue, sleep problems, pain, etc. -Katie M.
- Excellent points. It is crazy the RECOVER IVIG trial does not have an open label extension. A year of weekly visits is an enormous sacrifice. -John Bolecek
- Could not be more important to work to help Long Covid patients access off label medicines with their PCP or a specialist now. Then they can report into CURE ID. NIH Guidelines are a great idea to help provide suggestions to clinicians. his will help possibly improve quality of life for people in the meantime who may not have time to wait for years and years. -Michelle
- If researchers are not aggressive in trialing intelligent and novel treatments, patients will not wait around. I've seen ME/CFS patients for years pool together their money (sometimes north of $100,000 per order) to order unheard of experimental drugs in China, repackaged in supplement bottles to pass customs and distributed to patients across the US. "A fiber supplement" or "circadian rhythm changes" aren't going to cut it. Patients are DESPERATE and have no faith in the NIH. The NIH needs to earn the patient's trust BACK -Scott Daniska
- https://cure.ncats.io/explore/therapeutic-area/post-infectious-sequelae. -Erin Breland (she|her)
- There have been many questions regarding education of PCPs. I would like to add that there must be education related to the fact that there are many long Covid patients who had Covid in the first wave in 2020. We are 4 years out and still debilitated. my PCP recently said to me that "we can't continue to say this is long Covid this far out." Are

there plans to conduct and share research for those of us who have accepted that our debilitation may be permanent? -Gail Sprigler

- For those online can you share the CURE ID link: https://cure.ncats.io/explore/therapeutic-area/post-infectious-sequelae. -Mary Berghaus, HHS/OASH (she/her)
- MDs make up the majority of the speakers. -Isabel Silvestre
- How will RECOVER-TLC's submission review process differ from RECOVER-CT? Curious to know if there will be any differences/different strategies with respect to the review/selection process for interventions. Thanks! -Lauren Bradley
- Re study design: All of my doctors were shocked that all the Paxlovid trials didn't have an actual placebo group (they included Ritonavir). There is also the issue of length of time. I hope in future studies, confounding factors like this can be fleshed out ahead of time? And that we don't just give up on Paxlovid for instance because these three trials will show no efficacy? -Amy Engebretson
- Currently patients cannot get LDN covered by insurance because it is "off label" and must come from compounding pharmacies and they have to pay out of pocket often with money we don't have. We should be thinking about ways we can generate comparative effectiveness data to support use so that patients can actually get meds covered if we aren't going to actively trial them in RCTs. -Sarah Jolley
- Thank you, Julia, for acknowledging that there are patients with similar/same chronic illnesses without infectious initiating events, and thus investigations into mechanisms that aren't solely/directly caused by viral persistence is required. -Scott Daniska
- The room is full of high risk Long COVID patients who absolutely need to avoid reinfection, why is masking not required? What is the COVID protocol for this event? -Julie Lam (she/her) MaskTogetherAmerica
- My Name is Nicole Baca. I am an RN from San Diego who was infected with covid in june of 2020 from one of my patients. I was involved in a clinical trial at UCSD using Vyvgart/efgartigimod. After 13 months in this trial, I along with other patients went into "remission". Our study was abruptly cancelled 3 months ago. After speaking with patients, advocacy groups, and researchers it was due to resources and poor study design. Questionaries designed for autonomic failure patients that didn't always apply to us. This drug was a game changer, and we are now left getting sick again. I have regressed to where i was 2 years ago. We need studies like this, and study re-design done to push treatments like this across the finish line. Thank you. -Nicole Baca
- Comment to Dr. Vogel: I was pleased to see inspiritol listed as a potential treatment for Long COVID. It was listed under hypothalamic axis, but its usefulness is in that it targets multiple levels as it contains 5 nebulized ingredients, glutathione, NAC, B12, 1,8 cineole and B carophylene. So, it is useful as an immune modulator, antioxidant, anti-pathogen (including viral) as well as acting on the nervous system. I think we need treatments that act at multiple levels due to the complexity of this disease. -Selinl
- Is it possible to give clinicians treating LC patients a kind of emergency-prescribing-function to prescribe off-label use for LC and have insurance pay/cover? -Katie M.

- Given the lack of awareness about long COVID among primary care providers, is there a plan to distill the RECOVER and other research to distribute to PCP's and other physicians so patient care isn't subject to whether any given doctor is up on the research. -Wendy Shenk-Evans
- Completely agree with that comment about treatment follow up for CureID. We all know the placebo effect is real and it is compounded by this being a disease that fluctuates and features crashes and times of improvement. -Chris Nowak
- We need objective data collection e.g. autonomic testing, skin biopsy, micro-vascular endothelial measures for tissue oxygen uptake, neuro-inflammation, biomarkers, T cell profiling, GCRP ranti Ab, etc… -Megan McCoy
- What time do we reconvene? -Teresa Akintonwa
- One of my symptoms with long covid deals with breathing issues. is pulmonology addressed being addressed with long covid studies? -Robin Jones
- Could some please mute the in-room mics during the break? The distorted audio is rather agonizing. -PF Anderson
- Please STOP "yelling/spamming" about Masks/Masking in the conference room. There are an equal number of individuals who become upset/concerned when they see groups of masked people or are told to wear a mask – also based on their personal life experiences. Recognize that everybody is never going to be 100% happy regarding this topic. There are also many individuals who truly believe that masking is not effective (which is absolutely true if the individual wearing the mask has facial hair). If you truly believe that masking is effective, then by all means use one and trust that you will be protected. Simply respect people's individual choice (more-so if you are not in the room) – Please. -Kevin
- To the statements about masking at RECOVER testing sites; as a person who conducts such testing, I agree that participants do have the right to expect that their requests for masking during data collection should be honored/respected since they are the guests who are giving up their own personal time to participate in the study. I believe it is in our protocol to do this at all sites when personally requested by the participant. If this is not happening at your site, I would suggest that you ask to bring it to the attention of the site supervisor. -Kevin
- I will re-ask my question. How does one submit a request for support of a biomarker. Without any biomarkers, your goal of developing a therapeutic agent is equivalent to designing an automobile without a steering wheel. -David Vera
- What COVID precautions were put in place for the in-person participants in this meeting? -Hanna Kaufman (she/her)
- The researchers I work with at UMass Chan Medical would also like to know how to submit a request for funding to support their efforts to secure a potential biomarker. Who is the best person to reach out to about this? -Rivka Solomon
- We can't hear, FYI. -Ezra Spier
- Apologies, if someone already asked this question: How do we counter patient gaslighting? Would a brief consensus statement from this committee (or another appropriate governing body) for patients to take to healthcare providers stating that

post covid/ post viral conditions are biologically based conditions would dissuade gaslighting? Especially for the one-off visits where patients cannot self-select providers like ER or hospitalists. I have witnessed some very unprofessional conduct toward patient in these settings. Also helpful to include educational links in statement for anyone who might be interested in furthering knowledge. -Megan McCoy

- We are good now! -Ezra Spier
- Can I talk to someone regarding an imaging biomarker that we are testing now. It is FDA-approved for another indication, but needs to be tested for Long-Covid. With a small amount of funding we could test the agent within a short time frame. I would like to know if we should submit an R01, which would require a time delay. -David Vera
- Will summaries be sent to participants? I'm extremely sick with LC and physically couldn't tune into this morning's sessions, but they were VERY important ones. I'm literally dying to know what was covered. -Gillian
- Yikes, that's pretty embarrassingly inadequate. Not sure why you all might be having recruitment challenges with such a scientifically sound understanding of transmission and Long COVID! -RECOVER study dropout Hanna Kaufman (she/her)
- Oh, I forgot and should note for participants that The Sick Times is live blogging the conference, if you want info sooner than the NIH offering to release a summary in a few weeks… -Gillian
- How will you be including ME/CFS, both pre and post COVID regardless of potential triggers? -Cynthia Johnson
- Absolutely not good enough. This is shameful and it's impossible to take any of you seriously. -Hanna Kaufman (she/her)
- I hear the RECOVER AUTO trial is published. Can somebody share the link? -Terry Kerere
- Transgender people have consistently had the highest rates of LC in the US in the main dataset being used in this presentation and have not been named as a highly affected population in the overview of this panel. -JD Davids / Long COVID Justice
- Echoing Julie Lam's point, it's deeply troubling that "current government regulations" are being used as the baseline for accountability at a major NIH conference on long COVID. The fact that so many clinicians and scientists here aren't even masking—despite the presence of high-risk Long COVID patients—is nothing short of a disgrace. This gathering of the nation's top experts on long COVID should be leading by example, not disregarding the most basic and effective harm-reduction measure we have. The clinicians who treat masking as optional are perpetuating the very harm that high-risk patients continue to face across the country. Shame. -Ronak Kapadia
- I didn't see a response to my question. will those of us who have long Covid since 2020 be captured in clinical trials and information on our length of duration be included in clinical provider education? -Gail Sprigler
- What are we doing to include children in clinical trials as soon as possible? -Megan Carmilani
- How can you best include 65 plus population? Often not included but equally impacted. -Cynthia Johnson

- One critical aspect of defining the study population requires that we address the many outcomes of Long COVID. We understand that Long COVID is not a monolith, and that some patients develop POTS, ME/CFS, MCAS, Fibromyalgia and others. So, we need better ways to define "what kind of long covid" a patient has and that criteria will likely depend on what is being studied. I would encourage future studies that include cohorts with other IACCI's for comparison! -Elle Charlotte
- How will you include the house bound due to Long Covid and/or ME/CFS? -Cynthia Johnson
- Thank you to Angela for bringing up children! I am a parent and community advocate in global majority spaces that has been trying to educate on this but the mis- and dis-information is so strong. Wish Public health messaging was more accurate and accessible. -Karina M
- Angela, thank you for emphasizing the need for universal education about LC, particularly for children. -Ann
- Thank you to Angela for voicing the concern of multiple infections' impact on children development and adult aging. Watching people repeatedly get infected and the broader government insist we move on from COVID for the sake of the economy is extreme cognitive dissonance. -Gillian
- Can Dr. Saydah speak closer to the mic, please? -Julie Abella
- Can you remind the speakers to get close to the mike please. -Lucinda Bateman, MD
- How can we address the stigma surrounding pediatric Long COVID that prevents caregivers from seeking help from medical providers or schools, and how can we encourage families to feel more comfortable enrolling their children in clinical trials? -Megan Carmilani
- Sharon Saydah, why aren't you masking? -Gillian
- A trial specific to LC patients who menstruate - whether focusing on the reproductive effects/changes from covid and/or the symptom burden on this population generally. Women are disproportionately affected by LC, and young pre-menopausal/menstruating women are a huge portion of LC patients. They have already proven that people with PCOS were more likely to (1) get infected with covid and (2) get Long Covid. -Katie M.
- Sally, why aren't you masking? -Gillian
- Helen, why aren't you masking? -Gillian
- I am a school nurse (RN): Are we seeing the same rate of acquiring PASC with the newer strains of the virus? We are treating it like the flu in our schools with the exception of 5 days of masking when they return. But it is spreading like wildfire and most parents are not testing because it is not required anymore... and this is following the CDC guidelines! -Christie Welsh
- Chronic Neuro/psychological symptoms are my biggest symptom and concern in attending this conference. What would you recommend to me for the best outcome of translating my concerns to my treatment team at Kaiser Permanente? -Cheri

- Just FYI, for those listening via Zoom, there's a volume symbol on top left of screen that you can control volume as well as the volume on your device. Hope that helps those that are having difficulty hearing :). -Katie Gasemy
- What efforts will/are being made to include people with disabilities - whether a pre-existing disability or a disability resulting from Long Covid? Thank you. -Katie M.
- Question for Angela: How can we get public education systems across the U.S. to have more health equity and understanding about Covid-19 and its impacts on kids since so much of their funding is based on average daily attendance and their campaigns around "chronic absenteeism" is ableist and oppressive? -Karina M
- CDC web page has information on ME/CFS in children and includes information for teachers and schools, and families https://www.cdc.gov/me-cfs/children/index.html. Elizabeth Unger, CDC
- Some families may also resist diagnosis when there is no currently available treatment, due to fear of how this will impact their medical/disability/life insurance. How do you propose to address this to be able to include this population in trials? Shelley Ungrin, she/her
- Are there data surrounding the recovery period of the autonomic types of covid? -Lori Couture
- My worry is about LC symptoms worsening over time. Does not being diagnosed lead to poorer outcomes? What is the current understanding about preventing worsening of symptoms? Are trials being considered to find root causes of symptom worsening? What can be done to arrest a downward progression? -Ann
- Question for the panel: What would it look like to design a disability justice centered clinical trial for Long COVID? -Alison Cohen
- As a leader of a pediatric RECOVER hub, I identify with what Helen is saying. I have had long term changes that are very mild on the spectrum of long covid, yet I believe they are sequelae of my first COVID infection. -Lawrence Kleinman
- We often talk about stigma in a care or social situation. However, as a patient, I have experienced a political stigma when it comes to seeking Long COVID help. What are the drivers making Long COVID be viewed thru a political lens and how can it be dismantled? -Teresa Akintonwa
- Thank you! Doctors and patients do need to know that there are solutions to this. A protocol for primary care providers is needed so badly - even a one-pager on diagnosis, management and referral would be invaluable to them. (Speaking from a physician's perspective). -Amy Engebretson
- tagging onto the autonomic dysfunction question... for Dr. B and others, could cranial doppler be used as an outcome measure in POTS trials. this is based on the notion that orthostatic vitals are not always accurate and could be unremarkable over time (or with oral meds). Thanks. -Jennifer Minhas (she/her)
- I apologize if this question has been answered (I'm coming on late). This comes from a personal experience. In January, I found myself in the ER, and the RN nor the ER physician knew about LC nor ME/CFS. I share this because I've encountered this multiple times at ER, Emergency Clinics, and even at specialist offices where I'm going for a

symptom due to LC. My question is, what is being done to bring awareness? -Katie Gasemy

- We have protocols and tools to work with getting a diagnoses for ME. There is no robust program to educate the doctors and distribute these tools. The ME/cfs Clinicians Coalition has excellent resources that include the syndrome soup of co-morbidities such as POTS, MCAS...https://mecfscliniciancoalition.org/ -Kellyann (she/her)
- Thank you, Dr. Mady Hornig, for uplifting including ME/CFS. My question (again): Will pre-pandemic ME/CFS patients be included in the Long COVID trials? -Rivka Solomon
- what about wearable devices for patients at home? -Danielle Gillan
- Wanted to say that the sound quality from speakers in the room is very poor & hard to listen to, especially for folks with sensory issues. -Brian Vastag
- Has it come up in discussions whether trials can account for cases where both parent and child have long Covid? -Hazel
- Not uncommon for CT to use nurse visits to collect samples. Home diaries to collect PRO. Ways to keep attrition low and improve data collection. Can get at home EKGs and other data easily. -Megan McCoy
- I have documented 2 years if data to measure outcomes of physical mental emotional sensory and pharmacological interventions. -Danielle Gillan
- This may have already been addressed but I have a broad question - how can we ensure there is a long-term funding mechanism in place for baseline funding from NIH for LC & ME? A common theme reiterated these last two days is that this problem is not going away & will require further resources to address/conquer. -Billy Hanlon
- I should add I spent my first few days in hospital educating my nurses and physicians. As well as being my own advocate for care & treatment. -Katie Gasemy
- Pls can I be added to mailing list? How can interested folks be added? I just found out about this conference last night and had to get link fwded to me by site coordinator this morning. -Hazel
- As a follow-up to that question - should we expect NIH & NIAID leadership to prioritize LC & ME in their budget planning going forward - so that Congressional leadership can appropriate funding in the areas it's most needed? -Billy Hanlon
- What is the best way to compare pre-Covid ME/CFS, Long Covid and post-Covid ME/CFS? -Cynthia Johnson
- Hello, I am an RN from San Diego who was infected with COVID in June of 2020 while working on a covid unit. I was involved in a clinical trial at UCSD using Vyvgart/efgartigimod. After 13 months in this trial I along with other patients went into "remission". Our study was abruptly cancelled 3 months ago. After speaking with patients, advocacy groups, and researchers it was due to resources and poor study design. Questionaries designed for autonomic failure patients were used that didn't always apply to us. They did not capture the full picture of recovery. This drug was a game changer and it was working! We are now left getting sick again. I have regressed to 2 years ago. We need studies like this looked at again with patient input and study re-design done to push treatments like this across the finish line. Patients and doctors

involved believe in this study. Specifically, Dr. Goodman at the Metrodura Institute. Thank you. -Nicole Baca

- Hi, French HAS (Health Authority), will organize a scientific day on long covid the next Oct 14th. Many French organizations will participate such as Institut Pateur, Inserm, Institut Cochin, CNRS, HUG (Geneva) which are doing amazing works on physiopathology of Long Covid. Some of their works have been founded by Polybio. Does the RECOVER initiative is in contact with this organizations? Do you think it could be interesting to share the acquired knowledges and work together with the aim of understanding and treating LC? Ty very much! -Cityes
- For Dr. Hsue-Would you consider a more sensitive NASA LEAN test instead of tilt table? (Capturing more folks with POTS?" -Amy Engebretson
- we do not have the Ppt screen. -Joe John
- Completely agree with Ms. Stiles. Can we also include people with renal conditions please? -Julie Lam (she/her) MaskTogetherAmerica
- Thanks. My screen is showing JD Davids in a Japanese lattice triple wall!!! -Joe John
- Billions of dollars have been given to the States. Many states have not showed actual allocations of these funds. Is it being used wisely, and if not, can it be reallocated for Long Covid? -Alex Greeley
- Q: Alison (Barcitinib presenter), Thank you for including autonomic testing in your study design. I hope some sites are able to collect similar testing to Dr. Peter Novak's lab (his textbook for anyone interested: Autonomic Testing Oxford U. Press 2019). Can you please comment on how you landed on Barcitinib dosing which is higher than what is generally used in RA conditions in US? Is this from COVID indication? -Megan McCoy
- Q: Lauren, what do you think is time frame to manifest autonomic dysfunction in post covid conditions? Do you anticipate seeing it immediately on Autonomic testing or would take some time? TY. Megan McCoy
- No Q - PSA ! THANK YOU!!!! Thank you to all the researchers, clinicians, physicians, & everyone at NIH who are at the forefront of LC studies. I was a healthy, thriving 46 yr old in 2020 until April when I wasn't. Now LC, ME/CFS, Dysautonomia, Neuropathy, MCAS, Keratoconus (most recently undergoing finalizing diagnoses) MS. Thank you for the countless hours everyone is spending to perform studies to understand and hopefully treat LC and aim for prevention in the future. -Katie Gasemy
- Still hard to hear him. -Amy Engebretson
- The last two speakers have been difficult to understand. their audio keeps breaking up. -Ezra Spier
- I'm so sorry to have to say this again, but the audio is terrible. we can't really hear it on zoom. -Rivka Solomon
- the current speaker is barely intelligible. really disappointed that despite raising issues with the audio yesterday it is still very difficult for the thousand+ zoom attendees to hear the speakers let alone participate. -Ezra Spier
- One of my many symptoms with long covid deals with breathing problems, . Is pulmonology being addressed with long covid studies? -Robin Jones

- Question for Dr. McClure/NIH - Why hasn't RECOVER included an Ampligen trial if there are ME/CFS patients who have seen such improvement with this drug over the last 20 years? -Corinne Dorfman
- The arrogance to not mask at a conference specifically about people who got sick from COVID…. -Gillian
- THANK YOU JD —- FOR COMMENTING ABOUT PEOPLE NOT MASKING AT THE CONFERENCE!!!!! -Gillian
- Somewhat relevant to the current dialogue and also in response to the earlier question about whether medication changes are monitored within RECOVER - I work at the RECOVER site in San Antonio and we do keep track of changes in medications and supplements at each of the study visits (to include changes made in between study visits). We're going to use some of this data to look at combinations of medication that might alleviate specific symptoms or long COVID related conditions, which could inform future clinical trials. -Barbara Taylor (she/hers)
- Being an immunocompromised Long Hauler with chronic kidney disease, I am grateful to JD Davids for pointing out that the lack of a mask requirement is greatly reducing the accessibility of this event. This makes many people unable to participate in person. -Julie Lam (she/her) MaskTogetherAmerica
- Thank you, JD Davids, for your knowledgeable contributions and advocating for funding for ME/CFS, LC, IACC. -Susan Kandarian
- With regards to reinfection and prevention, when can a prophylactic monoclonal antibody be offered to people with Long Covid? Something like Evusheld before it was discontinued. Many findings are indicating a level of immune changes that could qualify people with Long Covid to be considered immuno compromised and they need something like this. -Michelle
- This year's CDC phone call survey has not a single question about covid or long covid. This is intentional suppression of covid data collection. -Gillian
- Thank you so much! What advocacy groups would you recommend for clinical trial teams collaborate with to better include trans and NB patients? Here in Kentucky, those groups face the same systemic extreme disadvantage and discrimination as many other Southern states. Ryan Weeks
- Thank you. It is the first sign for me that a clinician is taking Covid and Long Covid seriously and wants to protect patients. -Martha
- How are the investigators of the JAK-STAT trial screening for those with LC associated hypercoaguable states? Aside from excluding those with venous thromboembolism within the past 6 months? Is there a concern for increased thrombotic events with this drug? -Alice Perlowski
- as COVID appears to turn off DNA repair genes (ie p53) and may be oncogenic, how is this being monitored in the immunomodulatory studies? -Shelley Ungrin, she/her
- Thank you for your answer, I can share with you the link to the official HAS page of the coming scientific day : https://www.has-sante.fr/jcms/p_3530833/fr/journee-scientifique-covid-long-14-octobre . It provides all details about the agenda and

participants contacts. Sorry it's all in French but can be translated with internet navigator. Hope it will help. Kind regards. -Cityes

- How can all Recover researchers most efficiently be trained on ME/CFS, PEM (post-exertional malaise) and Dysautonomia before they design their studies? -Cynthia Johnson
- I was referring to the wearing of N95 respirators or better by all involved in trials. -Martha
- Viral persistence should receive much much more attention! How come it is not? We don't like its possible implications? -Zoltan Komar
- At least for ME/CFS, there have been small trials of immunosuppresive agents in the past using rituximab, cyclophosphamide, etenercept. The publications did not note clinical reactivation of infections as adverse effects. As compared for example with trials of immunosuppresants in MS. -Lily Chu
- JD, I wanted to say thank you for your comments, especially for pointing out that the majority of people in this conference room aren't wearing masks. I'm a Long Covid advocate watching at home wondering why. -Reda Rountree
- I second Zoltan's question. -Gillian
- will there be exclusions based on the length of time an individual has had long Covid; i.e. will this who had Covid in 2020 be excluded? -Gail Sprigler
- Why aren't step counts used as endpoints more? Wearables are relatively cheap and steps really show how much activity someone can do consistently. Props to Dr. Systrom for using these in the Mestinon / LDN trial. Can RECOVER use Lumia as well? -John Bolecek
- Can many of the patient-desired outcomes (reported by Dr. A. Cohen) be addressed by disability or QOL instruments? -Chris Wikman
- Fantastic points, Alison! I'm wondering if you can touch upon some of the challenges in measuring Long COVID symptoms across the lifespan, from pediatrics to geriatrics, and how these can be addressed? -Megan Fitzgerald
- Alison Cohen, Thank you so much for speaking out on disability justice/ safe accessibility to medical trials. -Julie Lam (she/her) MaskTogetherAmerica
- New COVID-19 infections were mentioned. What about COVID-19 reactivation in previously infected patients? -Isabel Silvestre
- I would like to echo the importance of COVID-safe study sites—this would not only protect the study participants, but also improve the quality of the studies, as re-infection would be a confounding factor. -Amy Geng
- It is very stressful for patients (or caregivers) to even have to ask people to mask; this is a constant thing that we have to do constantly in all our healthcare interactions. It is best for trials to require coordinators etc. to mask - or at LEAST proactively ask the participant if they would prefer that they wear a mask, and if the patient is wearing a mask automatically take that as a signal that they should put a mask on. Also - N95 masks - not surgical. -Chris Nowak
- having sites with clean air standards and masking is also trauma informed - those of us with long COVID who are intimately aware of the consequences often have significant

symptom exacerbation with reinfection - which we simply cannot afford. we already feel disposed of by public health and the public at large. going to a health care setting where people are not masked, where we know COVID continues to spread is a big trigger for PTSD developed during our journey with long COVID. -Shelley Ungrin, she/her

- Listening to Alison Cohen, I'm really struck that not only could these trial participation guidelines for patient safety and inclusion could ALSO serve to increase options for participation and inclusion for persons with disabilities broadly, not just people with Long COVID. Given that the stats for disability in the US population is typically around 1 in 4 now (1 in 3 in my state), this can only help to increase representation of disability as a population of interest to NIH. Thoughts on this and perhaps other additional positive outcomes of including these best practices as part of research methods broadly? -PF Anderson
- I understand the scientific control needs for the research. However, I wonder if involving the current medical care team that the study participate in the research process m ay educate the medical practitioners concurrently? -Sonia Lee
- I understand the scientific control needs for the research. However, I wonder if involving the current medical care team that the study participate utilizes to be involved in the research process m ay educate the medical practitioners concurrently? -Sonia Lee
- Can Dr. Hernandez explain in this setting why assessing / monitoring PEM is so critical in study designs? -Billy Hanlon
- I would appreciate please hearing Paul Lee discuss the FDA's plan to expedite approvals for LC treatments and working with NIH. -Gillian
- I understand the scientific control needs for the research. However, I wonder if involving the current medical care team that the study participant utilizes to be involved in the research process m ay educate the medical practitioners concurrently? Ie, actually conduct blood drawings, imaging, data collecting, etc. -Sonia Lee
- I got covid March 2020 at 33yo. Athletic, healthy, very successful in my career. Now 38, I'm on SSDI and rely heavily on my mom for care. I've tried very experimental meds. My life is on hold indefinitely and I cannot be a contributing member of society. I only plan on doing this until I'm 40. -Gillian
- Can you explain some of the acronyms being used? PGIC? PRO? -Jackson Riso
- Here is the PLRC and Body Politic proposal for meaningful involvement of patient advocates in the RECOVER Initiative (from November 2021), which I referenced in my remarks: https://docs.google.com/document/d/1OmF6PAUja_wW8skhyYOZbyDtnmyYxxqH5LUNfZQjy0o/edit -JD Davids / Long COVID Justice
- can we get a link to the PGIC he is talking about? i am finding a few versions online. -Rivka Solomon
- In every single long covid trial, there needs to be ME/CFS, EDS, Fibromyalgia, Multiple Chemical Sensitivity, POTS, MCAS control groups, so that information can be applied to those patients too, which is best use of taxpayer dollars. -Scott Daniska
- I hope the FDA recognizes the URGENCY of Long Covid. We are living as if we're dying every day for 4.5 years. -Gillian

- As a patient with Long Covid, I have significant post exertional symptom exacerbation. Additionally, I have “crashes”- a severe flare of my symptoms which put me in bed for days, which occur after infections/reinfections. How do you propose to protect the health of myself and other Long Covid clinical trial participants? Particularly with PEM and Covid reinfections a concern with attending clinical trial appointments. Have you considered mandatory masking? -Ylan
- I greatly appreciated Dr. Lederman’s recommendations to use PGIC, but I would like to caution that LC patients often report recovery or resolution of all symptoms, but only with careful questioning does it become clear that they have dropped multiple activities in order to achieve that asymptomatic state. Thus an assessment of functional capacity will be necessary too. -Meredith Cricco
- Many ME/CFS and Long Covid patients may be cancer survivors and/or going through cancer treatment. How can Recover work with the oncology community to see if there are cancer drugs/treatments that improve and/or aggravate the ME/CFS and/or Long Covid patients' symptoms? -Cynthia Johnson
- What specifically can be done in Recover trials to prevent making PEM worse and/or causing long term damage? -Cynthia Johnson
- For Dr Linda Geng, how do we move clinics around the country closer to model Stanford’s Long Covid utilizes? -Gary A, N Carolina
- Can Dr Davenport talk about PEM in adolescents and children? -Megan Carmilani
- PENE? Post-Exertional Neuroimmune Exhaustion? -Minghao Gong
- PRO= Patient reported outcome. PGIC = Patient Global Impression of Change (PGIC) defined as too to evaluates overall health status as perceived by the patient in a seven-point single-item scale ranging from 'very much worse…. -Megan McCoy
- Thank you Dr. Davenport for legitimizing PEM! That is my biggest challenge with long covid. -Lucy
- I would love to hear what Dr. Davenport’s favorite/suggested endpoints are! -Hannah Davis, PLRC
- And how we could include kids in clinical trials? -Megan Carmilani
- Instead of having these very expensive, lengthy trials, I'm wondering if it's possible that we can do some of this "clinical screening", which would be very short term trial of a bunch of different drugs to screen for what is most clinically effective because patients can pretty much tell you right away whether something is helpful or not. Would be nice to shorten this clinical trial period from 10 years down to like 2 weeks, because if every drug takes 10 years to test, then it will be thousands of years until we find whatever is most beneficial. -Scott Daniska
- Dr Paul Lee, great to see representation from the FDA here, thank you for your presentation. A question, what can the FDA do to prioritize and understand the sense of urgency for approving drugs and treatments for both Acute Covid (to lower the chances for developing Long Covid or Covid complications) and Long Covid? Long Covid is an emergency, why is it taking so long to accelerate ‘low hanging fruit’ things like extended courses of antivirals (20+ days for some people), additional antivirals available for Acute Covid, prophylactic monoclonal antibodies to prevent Covid infections in the first place

(i.e., Sipavibart), and repurposed drugs patients can try for Long Covid with their PCP or specialist while waiting for years for trials to have available outcomes that translate to practioners and Long Covid patients in the general population? -Michelle

- Paul, can the FDA help unblock patients to expand access for therapeutics that have and are showing promise in acute and long covid? Fauci talks about this in his book and Collins as well. “Parallel tracks” and removing more of the guardrails during this crisis. -Jon Douglas
- Does anyone have a link to the patient group guidance that Dr Lee mentioned? -Caroline
- For reference, a Long Covid Core Outcome Measurement Set was published late last year which was developed through a delphi process with large numbers of patients, providers and researchers. Many domains did not reach consensus so new PROs may need to be developed and validated, but this may be a good place to start from.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(23)00370-3/fulltext -Sam

- Is there somewhere that we can submit suggested measurable biomarkers? I think there are many we see over and over again, high lactate/low pyruvate, exhausted t-cells, low NK cell function, low deep sleep etc.? -Corinne Dorfman
- Comment- thank you Dr. Davenport for your discussion. As a patient, I was a 60 mile/wk bike rider until I had Covid 4 yrs ago. I haven’t ridden my bike for 3 yrs. due to head aches and muscle aches that occur about 20 mins after I stop riding (a stationary bike) and lasts for days. I had a mild case of Covid. I’m encouraged by all of the work being done. Faster iteration of the innovation would be greatly appreciated. -marcia
- It’s like triage — how can LC patients keep from backsliding is the first priority? -Ann
- Few people in the world mask or care about protecting people from repeat Covid infections. Many people with Long Covid cannot afford to live in a bubble. Imagine what a prophylactic monoclonal antibody, longer anti-viral courses readily available, more antiviral options, or combination treatment therapies readily approved and available for Acute Covid could do for current Long Covid patients and possible future Long Covid patients. -Michelle
- Q. FDA speaker. Is there an FDA guideline on validation process e.g. validation, which pre-existing validated tools can be used for different indication e.g. karmofsky functional tool used in oncology? -Megan McCoy
- Take a bow, Dr. Davenport! Thank you for being here today - and thank you NIH / NIAID for including this important presence in this 3-day gathering. -Billy Hanlon
- Thanks to all of you asking great questions- will try to respond to as many of them as possible if they don’t all get addressed during this panel. -Alison Cohen
- how do we design trials and studies for and including children with Long Covid and MIS-C with different presentations of disease (symptoms) across and in different ages? We must also try to understand how this can affect children’s development. -Greg Hayes
- The FDA needs to approve more peptides - many peptides have shown promising results. -Gillian
- can audio be unmuted? Thanks. -Ezra Spier
- were muted on the computer side. -Janice Stout

- Dr. Baden is muted. -Joseph Landson
- Dr. Baden is on mute. -Styrtb
- we cant hear you. -aslann
- We can’t hear. -Lindsey B
- Lindsey is muted. -Erin Breland (she|her)
- I believe we are missing the sound. -Amy
- the room is muted. -Alison Augustine (DAIT, NIAID)
- If he has started...he is on mute. -Lucinda Bateman, MD
- The presentation is muted for us. -Karin Dove
- sound is muted. -Lisa McCorkell
- Should there be sound? -Jessica Ross
- microphone is off. -Katie Gasemy
- sound is not on for online. -Elizabeth Unger - CDC
- We can't hear the room audio. -Mary Berghaus, HHS/OASH (she/her)
- those online can’t hear. -Alison Augustine (DAIT, NIAID)
- It’s muted. -Karina M
- Can't hear the speaker. Sonia Lee
- I can't hear the presentation. It maybe on my side Welcome
- The speaker needs to un-mute!! -Ray Ebert (NHLBI)
- I have no sound but see someone is speaking. -Laura.Swett@fda.hhs.gov
- still can’t hear anything. -Ezra Spier
- Excuse me but the microphone/audio is still on mute. -Heba Amer
- The speaker and the room are still muted. -Beth
- I do not hear sound. -Martha
- There is no sound. -Dori DataBae
- Zoom is muted. -Candace Rond, CCRC, BHC Research Manager
- Dr. Baden is still muted in case the meeting has resumed. -Li Chen
- Hello, the room is muted for those online. Thanks! -Caroline Pratt (she/her), CDC
- No volume. Can’t hear anything. -Upinder Singh
- Sound is muted. -Aimee Weiss
- Hello? Would you like to turn the sound back on? -Joseph Landson
- Please turn the audio on in the room. We can't hear. -Nicole Ford (CDC)
- please unmute the speaker. -Katie Gasemy
- is the sound off? -Gail Sprigler
- Sound please! -Amy
- The ROOM Microphone is muted. -Richard Gallagher
- Room 640 is muted. -russe
- Were you speaking? The microphone was muted. -Samarth Sandeep
- Need to unmute the speaker . -Alison Cohen
- why is the room still muted? -David Goff
- Please un-mute the room. -Ray Ebert (NHLBI)
- Please unmute the ROOM MICROPHONE. -Richard Gallagher

- Am I the only who can not hear? -aslann
- This is really frustrating and disrespectful to those of us who have taken time off work to participate. -Ezra Spier
- Could someone please unmute the meeting room microphone so Zoom attendees can hear? Thank you. -Styrtb
- Anyone? Bueller? Bueller? -Joseph Landson
- Please unmute for those of us online! -Erin Breland (she|her)
- It's on now. -Laura
- Yes. -Sonia Lee
- Its working now. -Dori DataBae
- Audio is working now, thank you. -Heba Amer
- Yes. -Katie Gasemy
- thank you! -Alison Augustine (DAIT, NIAID)
- @ Melissa charles - AVN is strongly correlated with steroid use . its caused by reduced blood flow through a single vessel. so the question is whether the microclotting and vascular changes seen in Long COVID might have increased this risk during your steroid course, and for the longitudinal study, whether this is happening without steroids. It has been seen during acute covid https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10092396/#:~:text=While%20the%20pandemic%20has%20not,be%20questioned%20in%20these%20patients. -Nancy Klimas
- Glad to see the Taiwan pediatric study is looking at vitamin D. It's critial for the adequacy of the immune response. Not considering it could be a confounder in other studies. -Roumiana Boneva
- In reference to COVID-19 safety, how can we get Institutions (healthcare, education) to support health equity for children- like making sure their policies and practices are based in science? How can we make sure these institutions create a safe environment for our kids to receive care and not have to contract multiple infections in the process? -Karina M
- Hi Stacey, I used a forwarded link & zoom did not require me to register…. will I still be added to list? -Hazel
- ME/CFS also impacts all ages and many have suffered from youth and for decades. How are the Recover researchers working on Long Covid children trials working with ME/CFS physicians and researchers globally? -Cynthia Johnson
- Gillian (or any speakers) able to elaborate on which peptides? And if any science? TY. -Megan McCoy
- Will comments in chat be published and available to review after each session? -Rebecca
- Placenta research would help us understand how this organ is affected during pregnancy, as well as reasons for potential early neurodevelopmental delays and changes. Can we start collecting placenta tissue in NIH RECOVER tissue repository? -Krista Coombs

- Follow up question: Is there a plan to study and include/design trials in children under 5 years old affected by long covid? Should they include MIS-C and KD? Long covid in these kids is quite different. -Greg Hayes
- Are you collaborating with school nurses? -Cynthia Johnson
- Comment- I think its so important to understand that every time children and adolescents get re-infected it sets them back for days, weeks, months. The trials have to take this into account. In addition - the follow up care, the longitudinal piece. -Nandini B Raj
- Are you planning to use currently existing COVID-19, MIS-C, and other seroprevalence cohorts? If so, how? -Jessica Ross
- Following up on Michelle M.'s comment about not being able to live in a bubble and monoclonal antibodies...and that the vaccine can induce Long COVID symptoms something like PrEP would be life-changing. -Cindy
- It is even more difficult for children with LC to access care, because very few pediatricians and specialists are willing to prescribe things off label to children for a novel disease. As treatments are selected for trials, what can be done to communicate those drug candidates to frontline clinicians, so that those not participating in trials can attempt to find symptom improvement while the trials proceed? Our kids are losing years that they will never, ever get back. -Reninger
- Given the variability of patients symptoms, what is the minimal number of participants & randomization ratio, to be able to detect any meaningful biomarker information/subpopulation effect? Dr. Vogel proposed 100 earlier, is it widely accepted? Any lessons from ACTIV? -Florence Herschke
- My team conducts an ongoing longitudinal COVID-19 seroprevalence survey (up to 6 timepoints including blood draws) since 2020 in Texas. We would love to collaborate. https://sph.uth.edu/projects/texascares/ -Jessica Ross
- What about doing short cross-over trials (placebo: drug swap to other group after time period)? -Megan McCoy
- We have enrolled over 4,000 pediatric participants (ages 0-18) and our participants are highly engaged. We ask questions about long COVID and have a large subpopulation of adults and children self-reporting long COVID symptom duration of over 12 weeks. Please reach out if you would like to collaborate. Jessica.A.Ross@uth.tmc.edu - Jessica Ross
- Thanks Stacey. May I ask why is this showing up as Private Answer? I am just want to make sure that I have not pressed anything on my end. I am hoping the comments are being shared with the panelists. Thank you kindly. -Nandini B Raj
- Would these trials be opened to Canadian pediatric population? -Nandini B Raj
- In our patient cohort, we only saw viral persistence in those patients being treated or having symptoms managed with steroids. -Clementine Adeyemi
- At Case Western Reserve University, We have a research mobile unit that is mainly used for recruitment of underrepresented communities in research. Amazing success with Recover enrollment as well as a multitude of interventional studies with oral agents. -Grace McComsey

- We have not yet addressed the unique challenges of long COVID among older adults. I am curious if there are studies specifically targeting recruitment among older adults and considering increased risk of dementia in mid to later life adults. -Anna MacKay-Brandt
- Will the chat be published, because lots of links have been shared in the chat. -Rebecca
- For Catherine Blish: Dr John Chia is an ID doctor in Torrance, CA has been studying intestinal biopsies for enterovirus for years. He might be someone you may want to connect with. -Kellyann (she/her)
- Dr. Sally Hodder...I'm Bottsie Hicks, a southern WV gal in Wyoming County...and I am THRILLED to know @WestVirginiaU has been selected as a #CAREforHealth pilot program! I am a pre-Covid person with ME/CFS of 17 years. I've been housebound for 3 1/2 years, but I'm IN if accommodations can be made! My PCP's practice is now under WVU Medicine. I e-mailed you this past Friday, so you should be able to get my e-mail from that. I'm also on Twitter/X. This forced-to-retire teacher would love to feel productive again. Thank you! -Bottsie Hicks. -Dell
- Have you considered recruiting various groups (eg ME/CFS for over 10 years, low income, no Covid related health care access, under 18 and over 65+, etc) now so that you have them available for future small trials? -Cynthia Johnson
- The education should include long covid, me/cfs, dysautonomia and chronic lyme. No child left behind! -Dorothy Hassler
- I am a NY State research scientist and co-investigator of a mid-sized NIH funded research program (n=1,.500 pre covid) characterizing brain health with neuroimaging and deep phenotyping of health, behavior, cognition. It is across the lifespan (age 6-90+). We are happy to pivot to understand long covid in our community ascertained sample. If anyone is local to Rockland county we are recruiting for a new wave as well. http://rocklandsample.org/ -Anna MacKay-Brandt
- Any other lessons learned from PANDAS, kawasaki, other pediatric dys-immune condition that could help guide adult/ pediatric LC trials and rx? meganmccoy
- I want to underscore @Mady Hornig's earlier point about the importance of proactively including ME/CFS in RECOVER trials whenever possible - including but not limited to children. -Rivka Solomon
- Can you start requiring all RECOVER universities and hospitals to teach and treat ME/CFS, Long Covid and related diseases/conditions if they are going to participate in research? -Cynthia Johnson
- Can look at hemophilia population and how important patient advocacy group(s) have been to help those folks trust and participate. -Megan McCoy
- Why wasn't masking made mandatory for this workshop? Are there other PCR/testing/ventilation practices being used in this current workshop that maybe can be adopted in some of the trial sites, if it is safe to be unmasked in? -Samarth Sandeep
- Comment about Trust- David Putrino has set a wonderful example at Mount Sinai with his team on the "Interdisciplinary Model of Collaboration and Compassionate Care". Long Covid has pushed the limits of science, medical, clinical, allied, lived experience to force us to work in an interdisciplinary way. We can no longer wonder in a multidisciplinary manner. It has to be interdisciplinary. -Nandini B Raj

- Sickle cell is another example where there is distrust that has been overcome through bridging relationships with patient advocates/ blogs etc… -Megan McCoy
- Thank you Dr. Hornig for your excellent comment that ME/CFS patient, who have a similar disease be included in all Long COVID clinical trials as a subset. -selinl
- Why isn't there a Community Based Organization on this panel to speak about the stigma and the limitations, especially when Howard University is a RECOVER site partner. -Teresa Akintonwa
- Community organizations and their benefits have been mentioned frequently. What can be done to support them (financially and otherwise) and provide guidance for reaching those struggling with long COVID who haven't already been identified, educating healthcare workers and other outcomes. -Jess Warner
- Specifically for North Carolina - why Duke is involved in RECOVER research, UNC has a Long Covid clinic, but there is no RECOVER site in the entire state? -Gillian
- How much research has been done on the impact of persistent inflammation from long COVID? -Belinda Edwards
- Specifically for North Carolina - why is it that Duke is involved in RECOVER research but no clinic, UNC has a Long Covid clinic but no research, and there is no RECOVER study site in the entire state? It seems to be politics between NIH and institutions, to the immense detriment of all the sick patients." -Gillian
- How much research has been performed on the impact of tachycardia on the body of those long COVID patients who are also diagnosed with POTS? -Belinda Edwards
- THANK you, Dr. Kanecia Zimmermann, for saying you will include long standing ME/CFS in your trials. -Rivka Solomon
- From Acute 3.5yr RECOVER cohort participant. I am thankful for you all! From a patient standpoint my big take aways today. CURE ID info. RECOVER TLC submissions portal. Loved hearing, Kanecia Zimmermann & Todd Davenport! -Meagan Vanni
- As an involved parent, we cannot even find studies/trials close to us to enroll in :-(I have had to travel to a neighboring state and only one child was selected to move onto the next stage of the study. We have not been able to access results of any bloodwork or cognitive testing either. We have an increase in long Covid symptoms. -Hazel
- I am also a RECOVER patient representative and patient. I thank everyone at NIH for your work to help us. -Belinda Edwards
- Thanks all! -Ezra Spier
- Comment: the VA had previously been setting up technology hubs in rural areas to provide care to veterans. I'm not sure if this is still in place but I'm sure there are learnings from how to make it work. Again, cross pollination of tribal knowledge would go a long way. -Marcia

Wednesday, September 25

- To Q&A Moderator: Pardon me. Please remind me on how best to submit a lengthier question that I'd appreciate the feedback on as a virtual participant. -Sonia Lee
- This may have already been addressed but I have a broad question - how can we ensure there is a long-term funding mechanism in place for baseline funding from NIH for LC & ME? A common theme reiterated these last two days is that this problem is not going away & will require further resources to address/conquer. -Billy Hanlon
- The portals for sharing treatment experiences so far have been great. Are there any portals for individuals to join a registry for recruitment? Self-characterization of demographics and symptoms would be a great opportunity for those who are already willing, and this could also serve as a hub for education and trust building. Also, for researchers to coordinate and more quickly ramp up studies. -Anna MacKay-Brandt
- Related to the previous question, how long is RECOVER-TLC envisioned to last: 2 years, 3 years? -Florence Herschke
- Billy, thanks for you support for ME community! -aslann
- Recruitment in a new population, even just extending from adults or teens to children or older adults is a challenge and sharing resources for outreach and recruitment through a registry would facilitate the pivot that many researchers are willing and able to do while also helping with the additional costs of this effort - which is so important and is not well-funded in our current mechanisms. -Anna MacKay-Brandt
- Does RECOVER leadership support the calls for a NIH office or center dedicated for infectious-associated chronic conditions (IACC)? -Billy Hanlon
- '@Billy Hanlon: This funding question is one reason we need a newly established NIH Office on Infection Associated Chronic Conditions and Illnesses. This would coordinate all research at NIH for these illnesses and make the work more cost effective. And the head of such an office could submit to NIH and Congress a proposed budget they think they need to handle this research each year. -Rivka Solomon
- Seeing how helpful this 3-day conference has been so far, does RECOVER envision holding a similar gathering like this in the future - bi-annually, annually, etc.? -Billy Hanlon
- "Re: surrogate endpoints – Dr. Resia Pretorius' group has found a biomarker that uses microclot analysis. However, it is currently only measurable by flow cytometry in a few research labs. How can the technology be leveraged to scale rapidly to clinic labs around the world?" -Ann
- Would RECOVER consider utilizing the 2-Day invasive CPET testing that is currently being undertaken at Brigham and Women's Hospital with Dr. David Systrom, in order to investigate PEM further? -Billy Hanlon
- How does something like step count from a wearable device like a Garmin work as an end point? If you gather average daily steps for a month before the drug and then after the drug? -John Bolecek

- Will there be a path to provide feedback later for those of us who require longer cognitive processing time or who were not able to watch the whole event in real time? Thank you. -PF Anderson
- Given the urgency of the need for patients, does the FDA envision to have an EUA process for Long COVID? -Florence Herschke
- That was an excellent presentation! -T.A.
- That was a very helpful overview. -Lawrence Kleinman
- For Dr. Cavaleri- why did you decide to focus more on treatment of Long Covid rather than prevention? What is the empirical basis for this decision? -Martha Young, JD/MBA
- Q: EMA/ FDA: Can you comment on fast track/ accelerated approval process and the anticipated time it would take to a get a new drug with good safety, tolerability and demonstrated efficacy to patients with LC? -Megan McCoy
- Could Dr Cavaleri say some more about what is practically being done at EMA to achieve the points he's raising? What mechanisms are in place that differentiate the urgency of this matter from other matters being dealt with by the EMA? -Emma Barrat
- Are the FDA and EMA coordinating to not repeat trials in US or EU (reduce redundancy) and ensure that unique trials get started and going? Collaboration helps everyone thank you. -Katie M.
- This Question is for all of you. I am a disabled pediatric oncology nurse lobbyist for equal access to care. I began monitoring my disease and interventions using a whoop. I use it differently than it was originally designed for elite athletes a made a calculation based on basic metabolic function. I have an energy efficiency equation. I have 2 years of data. Wearables are not a snapshot like scheduled assessments it’s my trends over time that has improve my quality of life and hrv. -Danielle Gillan
- For FDA: The use of steroids has been thought to initiate avascular necrosis in both of my hips and left shoulder. Is there any investigation of AVN related to PASC? Would internal inflammation contribute to this? -Melissa Charles
- Last week, Dr. Bertagnolli shared in a public appearance around RECOVER-TLC that “virus staying in the body is our leading hypothesis.” Is that view and declaration shared by other RECOVER leadership? -Billy Hanlon
- What improvement in PRO would you minimally consider as 'sufficient convincing evidence' to grant approval for Long COVID? -Florence Herschke
- Dr. Alain Moreau, PhD. has 11 MicroRNAs that can identify ME/CFS, Fibromyalgia, and Long Covid patients. The MicroRNAs can stratify Long Covid patients into 6 clusters, and they can identify drug responders for drugs like Ampligen. When will the NIH be calling for funding grants for diagnostic blood tests like MicroRNAs and the Nanoneedle for ME/CFS and Long Covid (which it has been refusing grants for the last several years)? -Andrea Martell
- Q: Will there be a NIH / FDA task force that recommends certain therapeutics for long covid as the research gets clearer, similar to the COVID19 NIH task force that disbanded earlier this year? There are many new therapeutics coming to market and combinations to be tested out quickly. How can patients tell FDA/NIH what is clinically meaningful in the case of off-labeling/EUA/combination/etc.? -Jon Douglas

- As an expert in my disease, it's the trends over time. Recently started LDN and the data shows immediate impact. My wear able prevents me from overextending myself prioritizing my recovery and managing my strain real time. -Danielle Gillan
- An important step appears that there is a lack of validated PROs and MCIDs for long COVID by specific disease domains. It appears that "repurposed" MCID values from single symptom manifestation of a non-Long COVID disease condition, would be much larger than what would be clinical significant in long COVID patients with multiple symptoms. We need a consensus document to be developed as soon as possible. -Sairam Parthasarathy
- Q: Will the FDA / EU consider a "parallel tracks" program where patients who cannot participate in a clinical trial obtain access to the therapeutics similar to what Fauci did with HIV/AIDS? Can the FDA / EU lower the barrier for already proven safe drugs that are yet to prove efficacy in Long COVID as well? -Jon Douglas
- Refer to the PFDD Guidance mentioned earlier by John and Paul. There are methods, both qualitative and quantitative, to establish meaningful change thresholds for a COA, which are then prespecified prior to the Phase 3 clinical trial. -Laura Swett
- Rather than trying to produce drugs from scratch, do you support screening the patient population (particularly ME/CFS patients who have been around for decades) for most beneficial treatments? -Scott Daniska
- Pre-ING meetings are great but they take months to schedule. Is there a pathway that can be created to speed the time for a meeting to be granted? -Jonathan Dinsmore
- Have you considered increasing the speed of approvals if AI agents have determined that a drug should be safe and efficacious? Perhaps this is not a reality now but may be in the next year or so. -Martha Young, JD/MBA
- in 2013, FDA had a "Voice of the Patient" conference for ME/CFS, and yet nothing happened since then for getting ME/CFS patients an FDA-approved meds. I wonder if FDA reaches out to industry or if that burden is on the patients and academic researchers? -Rivka Solomon
- The regulatory presentations are excellent. It seems repurposed drugs are the more likely, efficient and immediate priority for these planned trials - is this the general consensus or not? New drugs should also be studied in parallel as biomarkers identified, but that drug development timeline is not congruent with the need of large numbers of adults and children suffering. Now. -Roberta Debiasi
- HHS/NIH need to establish a new NIH Office on Infection Associated Chronic Conditions and Illnesses (IACCI), housed under the Office of the NIH Director. This new NIH office would coordinate all NIH research on ME/CFS, Long COVID, chronic Lyme, POTS, Dysautonomia, PANS/PANDAS, and other related illnesses. This coordination would make the work more cost effective incl finding biomarkers. The head of such an office should submit to NIH and Congress a proposed budget they think they need to handle this research each year. -Mark Camenzind
- My data includes treatment at Mayo for central sensitization HBOT zone 2 training determined by lactate testing and exercise dosing based on type 1 diabetic that became elite athletes. Inigo Sanmilan in Colorado has done years of research. -Danielle Gillan

- The EUA for approval of rapid antigen tests for Covid could have had a major impact on spread of disease, but FDA was very resistant to approving these tests? Can FDA be more open to novel therapeutic interventions? -Jonathan Dinsmore
- Q: If no declared public health emergency restricts the urgency from regulators, will there be federal agency advocacy to the HHS to consider declaring a public health emergency for Long COVID given the numbers you have heard here this week? -Jon Douglas
- I would like to echo the comments on delays to Novavax, especially to our kind representative from the EMA, who I believe are still in the process of approvals. -Emma Barratt
- Does the EMA have their own version of RECOVER trials, and if so, are they considering having any sites in the US (like we have abroad)? -Katie M.
- We know legislation was recently proposed in the Senate to dedicate further resources in this space, called the Long COVID Moonshot Act. Does RECOVER leadership have any comment on this legislation? -Billy Hanlon
- The general public has a belief that treatments require years and years of study and development before it can be deemed safe for patients. The accelerated development of COVID-19 vaccinations was a major reason for vaccination hesitancy. While our first speaker from the FDA mentioned the importance of diversity of demographics in studies and drug-trials. What can be done to reduce this public misperception and increase patient and public confidence in engaging with clinical trials? -T.A.
- Can FDA commit to a workshop? It is highly needed. -Jonathan Dinsmore
- Stacey, what are the panelists' names with Dr Cavaleri? Thank you for this!!! -Gary Anderson - N Carolina, USA
- Has there been any study on Long Covid resulting from the Immune modulated inflammation? -Sonia Lee
- Are there FDA scientists who can make themselves available to industry for communication and collaboration? -Jonathan Dinsmore
- Many intelligent people who have scientific knowledge to contribute to the pursuit to solving Long COVID were not allowed to speak at the TLC RECOVER event. What can you do to ensure that people who have useful scientific and medical knowledge to contribute have an opportunity to share them at future workshops? -Scott Daniska
- How urgent is solving the Long Covid crisis? Are there plans to reconvene this year? How is everyone staying connected and informed? Are there weekly meetings happening to push progress? -Shannan R.
- One of the concerns expressed repeatedly during this event has been the risk of reinfection during participating in trials, research, or routine medical care. There was a recent article by Fei Yu at al on H1 antihistamines as blocking transmission and/or replication in vitro and in animals that may have some potential here. I'd like to share some supporting anecdotal information from patient communities. Our patient support groups was discussing the study and realized it might potentially answer a question we had about why some people were constantly being reinfected despite masking and others weren't. We noticed that the people who were being reinfected despite isolation

and masking for necessary trips outside the home were people who were not taking antihistamines, and those who avoided reinfection were taking antihistamines. The most intriguing story came from one person who had repeated reinfections until being told to start an antihistamine cocktail, and then had no more reinfections. Some patients are taking significant doses of one or 2 H1 antihistamines, while others are microdosing with a greater variety or with a combination of H1 and H2. If this is not already being tested in humans that might be useful. -PF Anderson

- EMA: Are you aware of the BC-007 CT? -Megan McCoy
- Does NIH currently have a written strategy for drug dev in collaboration w industry?? Either for Long COVID or ME/CFS? -Gary Anderson
- Fatigue is NOT the biggest symptom. PEM is not fatigue. The ability to RECOVER after exertion is what is broken and what needs to be solved. Please use markers like step counts which are objective vs. PROs like "Fatigue" -John Bolecek
- Point of Order. AIDS is a Syndrome. The implication that ME/CFS is not a disease by calling it a syndrome is invalid." -Andrea Martell
- Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is a serious, chronic, complex, and systemic disease associated with neurological, immunological, autonomic, and energy metabolism dysfunction (Institute of Medicine, 2015), https://www.nih.gov/mecfs/about-mecfs#:~:text=Myalgic%20encephalomyelitis/chronic%20fatigue%20syndrome,Institute%20of%20Medicine%2C%202015). -Bridget Collins
- Berlin Cures has done trial using Aptamer drug for Long Covid, https://www.berlincures.com/en/ -Mark Camenzind
- "Question for the FDA: In 2012, the FDA did not approve Ampligen as a treatment for ME/CFS because there “is no blood test for ME/CFS”. Is a blood test required for Long Covid for FDA approval of successful treatments?" -Andrea Martell
- NAM (NASEM) calls ME/CFS a disease in their 2015 report. From their summary: “…Despite substantial efforts by researchers to better understand ME/CFS, there is no known cause or effective treatment. Diagnosing the disease remains a challenge, and patients often struggle with their illness for years before an identification is made…” https://nap.nationalacademies.org/catalog/19012/beyond-myalgic-encephalomyelitischronic-fatigue-syndrome-redefining-an-illness -Mady Hornig, MA, MD
- A recent summary of worldwide Long Covid studies is available at: https://www.ijidonline.com/article/S1201-9712(24)00176-0/fulltext. Perspective Volume 146107105 September 2024 Open access "The global clinical studies of long COVID" -Mark Camenzind
- Thank you to the fibromyalgia drug developer for your questions on how we can find funding and ways forward to bring treatments to LC (and ME/ fibromyalgia) patients given there is so little from NIH and industry for these devastating illnesses. I hope this can be addressed by panel and people in the room there. -Megan McCoy
- Thank you, PF, for bringing up these important points. I also want to call out that many pediatricians and other pediatric specialists like Allergists are often unwilling to trial

H1/H2 antihistamines for children and teens with Long Covid. I have real world experience with this at a major Boston teaching hospital. Perhaps a Pediatric clinical trial could be done. In CURE ID Famotidien (Pecid, etc.) is the second most reported repurposed drug. We also experienced reluctance to trial LDN - which is the most trialed off label drug in CURE ID. -Amy Torres Best

- Thanks Stacey. I submitted an inquiry on the website yesterday and look forward to hearing back. -Melissa Charles
- Follow up: When you say as soon as possible, do you mean this year? This week? A month? I aware that we aren't the only priority and afraid we are going to slip through the cracks, again. -Shannan R.
- Would it be possible for FDA/EMA to give an "opinion" on a product in development that would help industry be more inclined to fund? -Megan McCoy
- Why not use humans or AI to analyze all of the studies that used cluster analyses (PCAs) or had adequate sample sizes to reanalyze the data with such analyses of Long Covid and where the sample size is large enough in a future trial, request that a cluster analysis be included as part of a design so that some of the heterogeneity can be teased out of all existing and future studies? -Martha Young, JD/MBA
- Kathleen Banks asked a very important question. I'm a disability health equity researcher, and in our most recent study we noted that benchmarking tools typically use hospital or health system management as a proxy for clinician engagement, but do not actually engage the clinicians directly. Typically, they center the voices of administrators first, patients second, and clinicians not at all. -PF Anderson
- The survey that popped up from QR on screen requires you to first enter your email address. Is that so that folks only submit one entry? I'm just wondering if emails will be tied to responses in the survey (meaning no anonymity)? Thanks! -Katie M.
- Please include the link for the QR code in chat and in the Q&A -PF Anderson
- Could you please ask the speaker to go really near the microphone. So, we can hear what they are saying? Thank you so much! -Johanna Borde
- There has been an advocacy effort by Long Covid patients asking Congress for continuous Long Covid research funding. Senators Sanders wrote a Long Covid Moonshot bill (Senate Bill 4964). Does NIH themselves make an effort to communicate to the US Congress the urgency to address Long Covid and the importance of continuous funding? Does NIH explicitly request funds for Long Covid research from Congress?" -M M
- Just wanted to say a big thanks to Lizzie and Stacey (and anyone I missed) who has been answering and attending to our questions these 3 days - much appreciated!! -Katie M
- Yes, agree w Katie. The moderation from ALL has been exceptional!! -Gary Anderson
- Completely agree with Mady that ME/CFS has been clearly defined as a disease. Long COVID is still new and a similar consensus process and definition needs to be undertaken and formally established by the medical community. However, as the two conditions are so similar this should hopefully not be a difficult process. -selinl
- Selinl - I think the better question is why is Long COVID a separate indication in the first place? People have had chronic illness from lyme, mono, flu, H1N1, etc. for decades...

should there be an entirely new indication and repeat of all the same research every time there is a new pathogen that triggers this condition? -Scott Daniska

- Indeed. I guess what I was driving at is when it comes to Long COVID what role do these agencies see themselves taking in creating that better public communication? Most people have no clue when diseases "appeared" so there is an assumption that tall of their drug treatments were in the works for many decades. While this may be true, it doesn't have to be a Requirement to take that long. However, the world knows exactly when the novel corona virus appeared and have a perception of that timeline in the case of Long COVID. Such perceptions which are driven by scientific and drug development knowledge gaps are rarely within the scope and reach of trusted messengers to be able to shift. -T.A.
- COVID triggers Sjögren's Syndrome, Guillain-Barré syndrome (GBS), IgAN, diabetes, asthma, Rheumatoid arthritis and many diagnosable chronic autoimmune conditions, besides ME/CFS, POTS and a wide range of symptoms that affect our organ systems. As an IgAN patient, my indolent condition was exacerbated by an infection of SARS-CoV-2, causing hematuria, glomerulonephritis, and organ damage. The infection also triggered Sjögren's and sleep disorder, a more common Long Covid condition. I am in a clinical trial for an immune-modulator (Antacicept) that's created to control the molecules in the B-cell, in order to block the development of these abnormal antibodies IgA1 to prevent inflammation of the kidneys. Antacicept is a recombinant fusion protein designed to inhibit B cells, thereby suppressing autoimmune disease. I am sharing this because I would like to know what NIH RECOVER is doing about autoimmune disorders triggered by an infection of SARS-CoV-2. Is there any medical trial for immune modulators? -Julie Lam
- An observation, those questionnaires are tedious, repetitive, and painful to complete. Timing strange, and no privacy whatsoever if you have to call tech support. -Eileen E
- In Dr Baden's example, what does the community do if all those outcomes have a point estimate on the same side of 1.0, but the confidence intervals of all or most cross 1.0? -Carolyn T Bramante
- Will Recover-Vital data be available to qualified researchers for secondary analyses? If so, what is the timeline and process for that? -Anna MacKay-Brandt
- It is great to see all these organizations here talking and collaborating. While we wait for clinical trials, sometimes it feels like the FDA and other government organizations feel like 'hey, there's a vaccine (some people with dysfunctional immune systems are not generating enough antibodies though), there is an antiviral (5 days is not enough for Long Covid patients)… you will be fine until something is found.' That doesn't equate for people with Long Covid. Some of our immune systems are so dysfunctional after Covid, we need more support if we are to continue living and having any quality of life. Extended anti-viral courses and prophylactic monoclonal antibodies can CURRENTLY help with this need. Astra Zeneca has an updated Evusheld = Sipavibart, why is it not already approved by the FDA and being offered to immunocompromised and people with Long Covid? Why are extended courses of Paxlovid 10+ days not offered and suggested for immunocompromised and people with Long Covid? -Michelle M

- Regarding the QR code, thank you for the information that the link will be sent by email. Just for future reference, QR codes are not accessible for people with a variety of disabilities, and whenever a QR code is used, there should be alternative modes of accessing the content provided at the same time. I know you'll pass that along. Thank you! -PF Anderson
- A comment. As we continue to argue about endpoints, targets, and metrics, I'm reminded of Donald Rumsfeld after 911, saying we can't attack Afghanistan, because it doesn't have decent targets. We should attack Iraq instead; it has better targets. How well did that work out? How well will this effort work out, as we repeat the same Procedure and Process-bound approach? -Joseph Landson
- I second the nomination of Mike Peluso as QB! -JD Davids / Long COVID Justice
- The HIV blood test came before the AZT. We need funding for LongCovid ME/CFS diagnostic blood tests like 11 MicroRNAs, Nanoneedle, Raman Spectroscopy. When are we going to have a meeting about diagnostic blood test discovery? Cures in diseases are rare. Why are we discussing cures when we don't have a diagnostic test yet?" -Andrea Martell
- Three cheers for incorporating disability justice principles! https://www.sinsinvalid.org/blog/10-principles-of-disability-justice -PF Anderson
- Agree that patients who benefit from a drug during a clinical trial should be able to access it if it helps them. -John Bolecek
- Make that a 3rd vote of enthusiasm for MP as QB/LC Czar. -Mady Hornig, MA, MD
- Lisa, can you please share a link to the paper you've referenced? Lúcia Santos
    - Hi Lucia, here is the link to clinical trial paper Lisa mentioned: https://www.sciencedirect.com/science/article/pii/S0024320524005605 -Alison Cohen
- Thank you, Lisa!!!!!!!! Shannan R.
- Let me expound: Agree that patients who benefit from a drug during a clinical trial should be able to access it if it helps them. -John Bolecek
- Lisa McCorkell said everything! -Rivka Solomon
- Great job, Lisa!!! Thanks for sharing all of that information. -Brittany D. Taylor
- Can Lisa share her slides publicly? -Rivka Solomon
- I also nominate Michael Peluso - terrific job Lisa! -Billy Hanlon
- Amazing presentation Lisa! -IBekirov
- Ditto re: nominating Michael Peluso. -Rivka Solomon
- Wonderful presentation from Lisa McCorkell! Covered so many critical issues. -Lawrence Baizer
- Yes, hopefully slides can be shared as I missed the beginning of that. Awesome presentation & energy! -Cheryl
- Emphasizing the need for pediatric and life course research! -Lawrence Kleinman
- Lisa McCorkell - so powerful!! Can't thank and cheer that presentation enough. Katie M.
- I appreciate this conference and these presentations very much. However, I've missed whether anything concrete has come out of this conference, or will. Will new trials be

launched? Will current ones be modified? As Lisa and others have noted, there is no time to waste—we patients are desperate. Thanks. -Lila

- Treatment trials are critical. We should not lose the potential for other designs to assess efficacy when data capture allows it, I reference a landmark study of case control studies by Gene Shapiro of Yale: https://pubmed.ncbi.nlm.nih.gov/14872178/ https://jamanetwork.com/journals/jama/article-abstract/373850. -Lawrence Kleinman
- Q: Qualitative data can be more challenging than quantitative. Is there someone to address this here or in near future? Other questions for patho-physiology of enthesopathies we are seeing in patients e.g., neuro vascular dysfunction, cerebral regulatory impairment, blue limbs/nail beds, reflecting poor tissue oxygen uptake (not reflected by a normal pulse ox), that may be contributory or causal of PEM etc…" - Megan McCoy
- Instead of focusing on only viral persistence and host immune response (both of which I can guarantee will not lead anywhere), how about focusing on the DAMAGE that viral events will cause, even if the virus is eradicated from the body. If you don't consider that, you will never be able to make an understanding of the environmental factors these patients become susceptible to. -Scott Daniska
- Does Recover plan to utilize EHR from every person with Long Covid that wants to share his or her EHR? Utilize AI learning to find out more about unifying factors? The All of Us study and Cancer Prevention Study is doing something like this, requesting bio samples from patients at home and access to their EHR's. Most Long Covid patients have had tons and tons of testing done. Can all of these test results be leveraged for information? -Michelle M
- Thank you, Laurie Gutmann, for pointing out the importance of building trust with the patient communities. RECOVER-TLC brought researchers and patient advocates together— it is a crucial step forward. But our government's research initiative is still a long way from addressing the crisis and one of the core issues is the lack of awareness and lack of public guidance to prevent infection and transmission. The only way to protect people from onset and repeat infection is to use effective mitigation tools, including masking. The only way to prevent Long Covid or relapses of these debilitating post-COVID chronic conditions is to avoid infection. Knowing that SARS-CoV-2 is an airborne virus, spreads mainly through aerosols and infected people who are asymptomatic, masking should be a requirement for medical trials and all in-person events like RECOVER-TLC. -Julie Lam
- We know NIH cannot lobby, but all patients, caregivers, advocates, researchers need to support Bernie Sanders Long Covid Moonshot. This could help fund long term Long Covid/MECFS/IACCI studies that are so needed. Details at: https://www.sanders.senate.gov/press-releases/news-sanders-introduces-historic-moonshot-legislation-to-address-the-long-covid-crisis/ See also SolveME.org, MEAction.net so we can get the funds that are lacking to Cure Long Covid, ME/cfs etc. - Mark Camenzind
- What he said about the IVIG trial being limited to folk with MECFS criteria, the LC folk I know who have received the greatest benefit from IVIG have not had the fatigue issues,

but instead of neuro and autoimmune issues. That might be another population to test. I also really LOVED him saying that we need to do subtype analysis and find out what is in common among the folk who respond positively compared to the folk who respond negatively to any of the proposed treatments. Bravo! -PF Anderson

- Wearable Devices. Real time data. -Danielle Gillan
- Regarding issues surrounding trial recruitment, what can be done toward engaging (and investing) in community organizations who are in a position to provide outreach to educate providers, health departments, and more importantly, those individuals who have been identified as at risk for Long Covid (BIPOC & LGBTQ+)? -Jess Warner
- What is the name of the agent portal submission site? -Rowan Walrath
- How will data on the portal submission for potential agents be shared with diverse communities to ensure that patients from these communities have an opportunity to comment on desired interventions/trials? -Sarah Jolley
- Dr. Moreau's 11 MicroRNAs can cluster Long Covid patients into 6 clusters using Random Forest Analysis - we learned this in December 2023 at the NIH Conference. HE should have been invited to discuss this. -Andrea Martell
- FYI, the current speaker is almost impossible to hear/understand. -Ezra Spier
- Maybe I am alone in this thinking, but I would rather trial be unaccommodating and demographically skewed, if it means that research would be QUICK and EFFICIENT and get real treatments that benefit quality of life for patients sooner. -Scott Daniska
- How does RECOVER-TLC plan to engage/involve patients and caregivers going forward? Is there a way for either individual patients, caregivers, or groups to "volunteer" or "sign up" to do so? -Katie M.
- Dr. Bertagnolli announced the CARE for Health™ program at a webinar at VCU last week. One important goal is to "Conduct research addressing issues important to diverse communities, particularly those underrepresented in biomedical research" with longitudinal collections of clinical data and informing evidence-based care. How will this program be integrated with others being (or that will be) launched through NIH RECOVER/RECOVER-TLC? Seems like a critical multidirectional path for clinical research efforts. Thanks! -Mady Hornig, MA, MD
- RECOVER-TLC is aware of the CARE for Health program, both are high priorities of the NIH. While no formal collaboration has been established to date, there have been discussions. Let's Go. -Danielle Gillan
- Regarding exploratory biomarker studies in RECOVER TLC trials (and trials in ME/CFS and other conditions that could have shared mechanisms), I want to strongly advocate for assembling a subgroup of experts to design biomarker and mechanistic studies across RECOVER TLC trials. Efforts should include not only finalizing SOPs for acquiring and processing samples, but also dedicating careful attention to designing the assay runs that will be performed later, to reduce and control for batch effects. RECOVER's existing SOPs are excellent and should serve as a solid starting point. It may not be feasible for all centers to process samples locally; however, centers with this capability should be funded to process samples locally, using these validated SOPs. This will be particularly important for blood cells (where functional assays might be studied), for special

populations of cells such as neutrophils and platelets which require specialized processing, and for accurate measurement of labile analytes. -PJ Utz

- Amen!!!!! -Danielle Gillan
- So powerful -Danielle Gillan
- ME/CFS is 1 out of the economy that's sick, and 1 out of the economy to take care of them, and that's why it's now a 1/2 trillion-dollar problem. Neglecting ME/CFS is just compounding a mistake. -Andrea Martell
- Given that RECOVER appears to have spent the vast majority of its money on observational studies and clinical trials how can RECOVER can help in the future uncover the much-needed biomarkers needed to support clinical trials? -Cort Johnson
- Hello, if I may ask, how can patient representatives/advocates be incorporated into basic science research? Should we seek the same avenues and committees that are available for clinical trials or are there specific accessible resources for those conducting basic science research on Long Covid? Thank you so much in advance! -Heba Amer

- As some who has had Long Covid for almost 4 years now and a healthcare worker, I second everything this young lady is saying. It is so had to work and try to keep track of everything, and find help, and get off work, and to even drive.
- Thank you!!! -Danielle Gillan
- Messed up the last comment: Agree that patients who benefit from a drug during a clinical trial should be able to access it if it helps them. Whether Ampligen, BC007, IVIG if a drug helps someone in a trial but its not approved or covered by insurance, the fact that the trial helped the person should be all the evidence needed for the person to continue to access the drug. -John Bolecek
- Agree that Dr. Alain Moreau's work is important and he should be brought into the RECOVER research work. -Rivka Solomon
- These comments are a poignant reminder of the importance of the "digital pathway" for study/trial participation to be a core foundation of the next iteration of RECOVER. The digital pathway was a bolt-on about 18 months after the launch of RECOVER once sites and SOPs were already in place and was very challenging to shoe-in after the fact. -Vik
- Given the need for biomarkers and the lack of NIH funding, thus far, for long COVID outside of RECOVER - will NIAID and NINDS commit to funding numerous RFA's to dig into long COVID pathophysiology and uncover those biomarkers? -Cort Johnson
- In addition to preventing false discovery, it seems that an important reason we designate a primary outcome is to minimize missingness for that outcome. Missing data is an important aspect of grading evidence for risk of bias. However, with so much we need to understand -- How do we balance of breadth of questions we should answer but maintain high internal validity with low missingness? Is it enough to report missingness? Impute missing data? Or do we need to limit the data collected in each trial?" -Carolyn T Bramante
- NIH Guidelines reach really far. Having support from NIH Guidelines for possible Long Covid medications, extended anti-viral courses or monoclonals, possible tests to try for Long Covid (capture these test results in EHR access for data collection) and treatments

that are in process which patients could try with their providers if willing (report into CURE ID the results). -Michelle M

- Thank you to this woman advocating for her mother. There are NIH funded studies that want to include long covid into our protocols. We are a huge resource and don't need re-invent the work we have already done in our program for community outreach. We need to think about how to work across the institutes and existing studies. We are an ongoing NIH funded research program and will be looking to collaborate as well. Anna MacKay-Brandt
- Will the 'patient story' link be kept open for a while after the conference is over? Eileen E
- Just to follow with the pediatrician question- we collect and biobank samples at every timepoint baseline, every 6 months for 3 years in our 1000 subject prospective longitudinal pediatric Covid outcomes study to allow for these evaluations. -Roberta Debiasi
- Would it be possible to have a group of Key Opinion Leaders to help guide upcoming trials? Folks who are multi-faceted in science and protocol development as well as direction on analysis. TY. -Megan McCoy
- Not a question but just a comment that experts should also be leveraged when measuring specific constructs in trials. Cognition should be measured and interpreted by neuropsychologists. There are too many poorly characterized studies because of suboptimal measured endpoints. -Jackie Becker
- Are there efforts to harmonize trials through other sponsors (e.g., PCORI) and European Union? -Sairam Parthasarathy
- I've heard from participants in the original RECOVER study that it is ending (3 years) and they are having final visits. Why isn't the study continuing given the fact that LC ongoing? At least give patients the option to continue please. -Katie M.
- Huge thank you to every single person who took part in this collaboration! Thank you to the people who set this up, moderated, and took the time to bring their ideas forth and take-home ideas to progress things further. Please have this type of collaborative meeting again soon. Much sooner than a year. -Michelle M
- On same lines with representative stakeholders e.g. investigators, patients, advocates, clinical trial coordinators, industry, gov't? -Megan McCoy
- I would like to suggest that NIAID put up clinical guidelines for long COVID, akin to the HIV/AIDS guidelines and NCI's PDQ for cancers. This would be an invaluable resource for patients and health professionals regarding definitions, phenotypes, diagnosis, tests, treatments. Patients could refer their health care team to this—it would go a long way to help educate providers who are not familiar with long COVID. There is widespread lack of awareness in the medical community that an NIH website could ameliorate. -Amy Geng
- Can someone please share the referenced "patient story" link? -Amy
- Where can I find the link, please? -Eileen E
- Is it safe to say that NIAID is now leading RECOVER essentially, where it originally had been led by NHLBI? Asking for clarification if you are able to. -Billy Hanlon

- There needs to be funding coming from not only government, but all non-profit funding organizations throughout the US, so that multiple sources can be leveraged. -IBekirov
- It's been brought up, but if we did a better job of linking research to ongoing clinical care such as through the AHRQ Long COVID Care Network, we would have structures for care navigation, use of digital supports such as telehealth which are supports that we aren't using currently. We are hindering ourselves by not having our research programs so divided from where patients are receiving care for long COVID. -Sarah Jolley
- The advocacy community needs to gather all possible funders together perhaps in a meeting. -IBekirov
- Has NIH considered encouraging foundations with funding also support this work? -Andrew Wang
- An opinion, Patient Perspective: More important than anything is getting options out there in terms of treatments / pharmaceuticals that Long Covid patients can try as soon as possible. Time is one of the most important factors. -Michelle M
- What is RECOVER itself doing, without relying on patients to do the heavy lifting, to amplify the research we have now, even outside RECOVER like within the NASEM Definition report to the very funders/ decision makers to advocate for, justify, and obtain funding? Patients cannot be the only ones fighting, they need to hear from all fields and stakeholders. We do not have the time. -Karyn Bishof
- I hope that would be merit based, as opposed to having the same old faces represent these conditions... There are a lot of brilliant untapped minds out there that are desperate to contribute, and what I see from all these advocacy events is only the same old voices get spoken repeatedly. -Scott Daniska
- thanks! -Eileen E
- I want to note that I am a new RECOVER patient rep and even the process of signing up as a vendor via RTI has been incredibly burdensome and unrealistic for many Long Covid patients. I know of folks who have had to drop out because they cannot navigate the bureaucracy. This is a huge barrier to patient engagement. -Ezra Spier
- Also, future meetings should include industry. -IBekirov
- A lot of us have paid for gut biome tests to assess our ibs type symptoms. Biome Sight is a popular company, and they have a large amount of data on long COVID dysbiosis from thousands of patients. Please reach out to them and other biome companies to utilize their data. There are consistent patterns in low/high gut bacteria. -Sara
- I second Sarah’s comment. -Shannan R.
- Is RECOVER now being housed at NIAID? And what does that mean for the ME/CFS work being done at NINDS? -Rivka Solomon
- thank you so much to everyone who planned, attended, and contributed to this conference. as a person dealing with LC I found hope in hearing from all the committed professionals, hearing the experiences of other LC folks and seeing how genuinely most professionals listened and learned from people struggling with LC. I learned so much and have so many links and topics to further reesearch. Thank you thank you thank you. -Linda Patton

- In order to save resources and level the playing field, I hope you'll consider all-virtual meetings as much as possible. -JD Davids / Long COVID Justice
- Seconding JD's request for open virtual meetings. -PF Anderson
- I endorse the idea of an annual meeting similar to this one. I would also like to suggest a similar, shorter, perhaps 1 or even half day meeting, every 6 months or so, as research external to NIH does appear to move relatively rapidly, and that may inform approaches and priorities. And on the topic of inclusivity, I want to explicitly mention that intersex participants should also be recognized when collecting demographic data, especially given the seemingly important role of hormones in this condition. Thank you again. -Emma Barratt
- Did I hear right that Dr. Marrazzo said "I will be having a team, reporting directly to me, working specifically on this...housed in the Office of the Director"? Asking for clarification. -Billy Hanlon
- @Billy, I think Dr. Marrazzo meant the Office of the Director of NIAID, not the Office of the Director of NIH. -Rivka Solomon
- Can ME/CFS research be joined under her office? Why silo these diseases? It would be ideal to learn from the existing ME/CFS research and not start from scratch. -CD
- accessibility in this population also means recognizing that people need "accessibility" for new onset cognitive dysfunction, vision impairment, etc. that means websites/apps need to be accessible and forms need to be accessible. -Bridget Collins
- Love Emma's suggestion. Also, perhaps partner with Project ECHO on dissemination of Long COVID findings, and have RECOVER researchers present for PCPs and patients there for translation of evidence. And get Project ECHO to put their videos in YouTube for broader discovery! -PF Anderson
- Will ME/CFS and the ME/CFS Research Roadmap also be in your office to promote collaboration? -Cynthia Johnson
- Dr Mazzarro, your skill and position makes it possible to save millions of lives. Thank you. -Susan Kandarian
- Which institute will fund the small mechanistic/exploratory clinical trials? What mechanism? -Sairam Parthasarathy
- Points I hoped to cover at the mic: We must grease the pipeline from clinical case reports and patient/clinician experience to clinical trials. Must accelerate integration of RECOVER clinical trials initiatives with newly announced CARE for Health (Communities Advancing Research Equity for Health) program and others, including PCORI. NIH must solicit patient/community/expert input to develop specific PROTOCOLS that ensure: Inclusion/Equity/Respect & Support for Diverse Populations (including but not limited to those with other infection-associated conditions). Study Design (when/how samples are collected; our ME/CFS studies always collected controlling for circadian factors/time of day, season, geography as well as timing sample collections *after* surveys/Q completion (serves as potential PENE inducer for maximal info). Sampling - timing of collection (as per 3b), local pre-processing and additional processing prior to cold/frozen storage. LOCAL + CENTRAL BIOBANK SUPPORT. Also, whenever feasible, RETURN

biological and other data to patients following clinical trial participation. Thanks. -Mady Hornig, MA, MD

- Will Recover-TLC leadership have a meeting reviewing all the learnings and the Q&A from these past couple days? What is the best way to reach out to them with further insight/feedback in the future? -Michelle M
- I know this question won't probably be answered today. PEM (post exertional malaise) is the hallmark symptom of ME/CFS. Before Long COVID this symptom was unique to ME/CFS. I wonder what is the difference between ME/CFS and a large subset of the Long COVID? Regardless, ME/CFS researchers who have been working for years (with very limited funding) on a condition that is incredibly similar to Long COVID. It would be of great benefit to include expert ME/CFS researchers and clinicians in whatever capacity that you can. There are decades of research and experience to learn from. Thank you. -Amy
- Thank you for bringing the "trust issue" up. This conference is an excellent step in the direction of rebuilding trust between federal agencies, healthcare, and the public. -Gary Anderson
- I beg to differ. Project ECHO is doing great things with PCP training on Long COVID. The problem is that PCPs don't know they're doing it! -PF Anderson
- is there a list of analyses already being run on the samples in the biorepository, or already been considered and rejected? we want to avoid duplication or taking the time to submit proposals for ideas that have already been rejected. -Laura-Isobel
- Perhaps RECOVER could help profile or promote ProjectECHO's LC training resources? -PF Anderson
- Regarding developing and updating long COVID treatment guidelines - there has already been a lot of work in this area through the AAPMR PASC collaborative to take a look at so as not to reinvent the wheel. -Laura Malone
- Since the CDC is basically non-existent, can the NIH create a Long Covid public awareness campaign? Patients can help. -Shannan R.
- What is the involvement of NICHD in the leadership and planning process? Thank you. -Lawrence Kleinman
- Fantastic goal – Developing and updating LC treatment guidelines. -Ann
- For primary care professionals and insurance-are there options on forms including case notes that include long covid? -Linda Patton
- One of the last slides mentioned Long Vivid in one bullet point and in a nearby bullet point used the word 'spectrum' regarding, I think, testing. the first day's first speaker spoke of the definition of Long Covid & the desire to use the patient created name 'Long Civic' Please consider adding the word 'spectrum'. Long Covid Spectrum - might better suggest how large the umbrella title is. -P. Charlie
- https://www.aapmr.org/advocacy/current-priorities/long-covid-pasc/multidisciplinary-quality-improvement-initiative. -Laura Malone
- Where can I find any information related to Mentorship programs? -Minghao Gong

- SAMHSA also has a role in Long COVID (i.e., behavioral health impacts)....https://www.samhsa.gov/blog/behavioral-health-impacts-long-covid-policy-action. -Mitchell Berger
- Some of us have been waiting for 40 years for to hear what Dr. Marrazzo is saying. I hope these words translate to action. Thank you to all who organized this meeting. -Rivka Solomon
- Thank you!!!!
- where is the patient story link? -Destry
- I am a young ME/CFS investigator and would seek help for any potential opportunities to support myself in further my research in this area. I was facing issues with funding myself and I really would like to gain more access to opportunities to continue this research endeavor. Thanks! That is why I want to understand if any mentorship, scholarship could help? -Minghao Gong
- This whole thing was fantastic. I appreciate being able to attend on behalf of Black COVID Survivor's Alliance, Inc. -T.A.
- As a caregiver I just wanted to say THANK YOU!!!! as I've felt alone in this walk with my husband who has Long Covid since the 2020. It's so encouraging to now that we have a voice & there are others out there. SO THANK YOU FROM THE BOTTOM OF MY HEART!!!! -Sharon
- Thank you for organizing this conference and bringing us all together - academics, industry, government, community and patients. Very very appreciative. -Sachi Ushihara
- I've had Long Covid for 3.5 long years. It's been brutal, but this conference has given me hope. Thank you to all who participated. -Kyle Creane